Brainstem Tumors: New era or more of the same?

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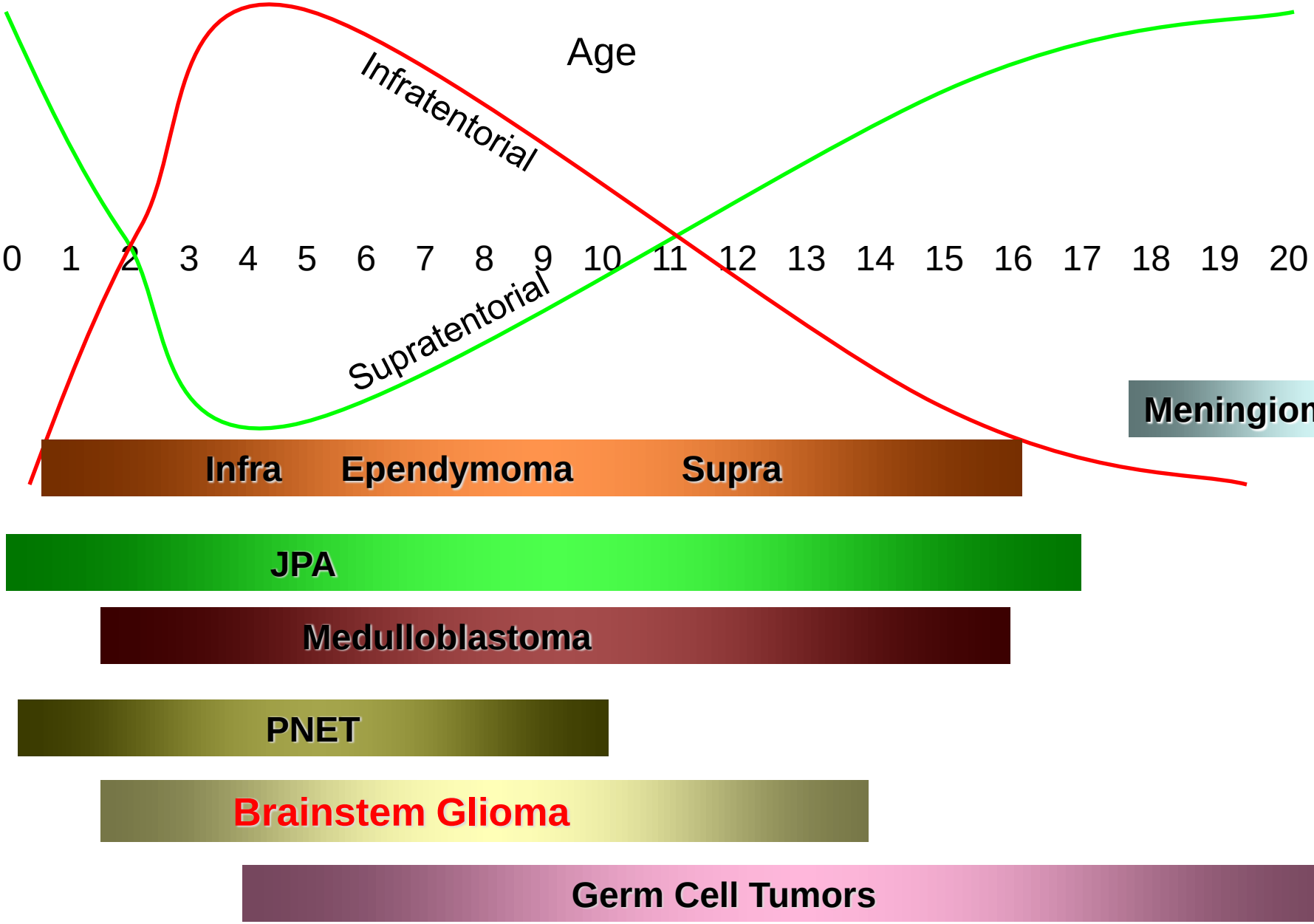
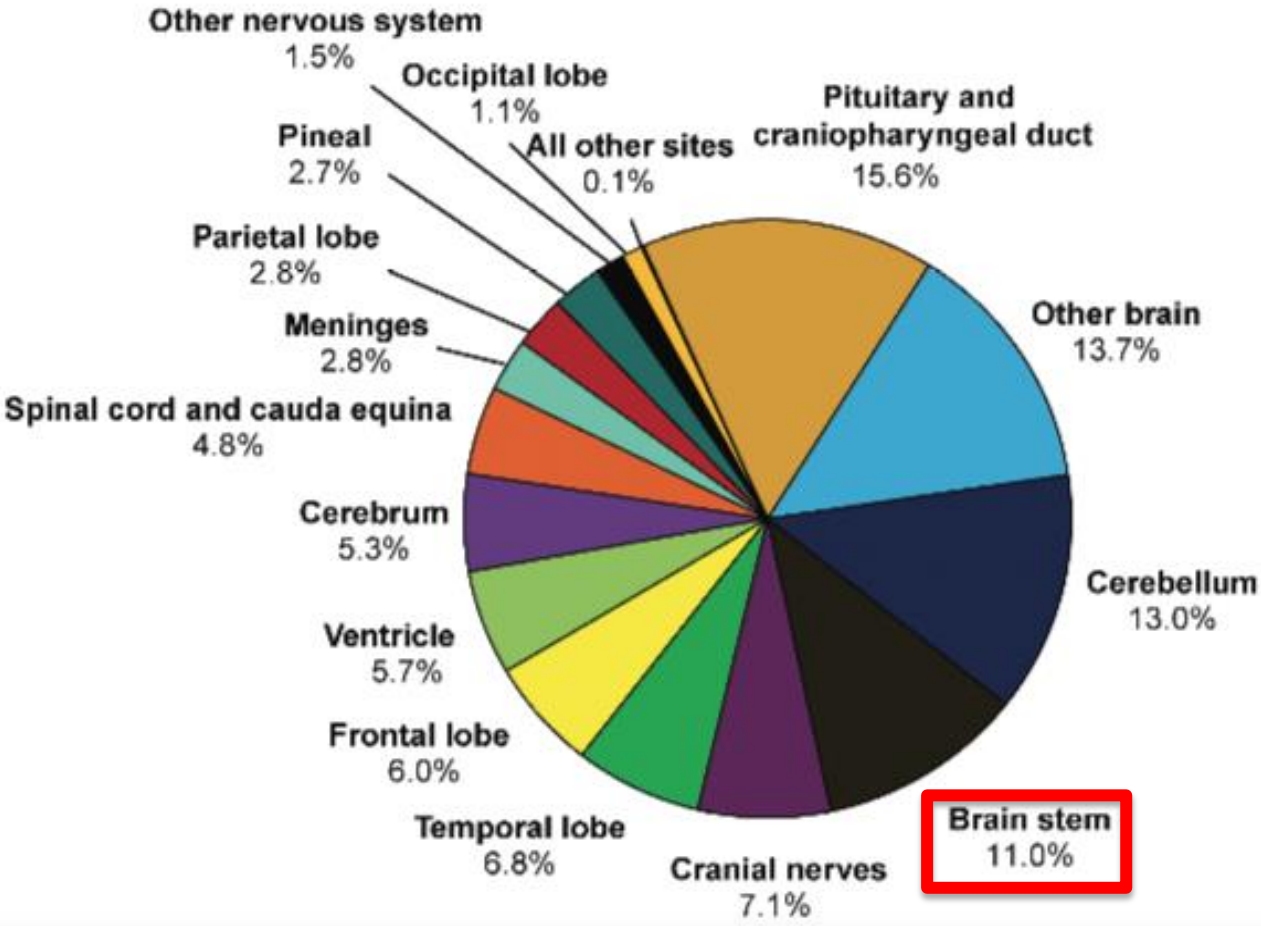

Age
Infratentorial
Supratentorial
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Meningioma
Infra
Ependymoma
Supra
JPA
Medulloblastoma
PNET
Brainstem Glioma
Germ Cell Tumors



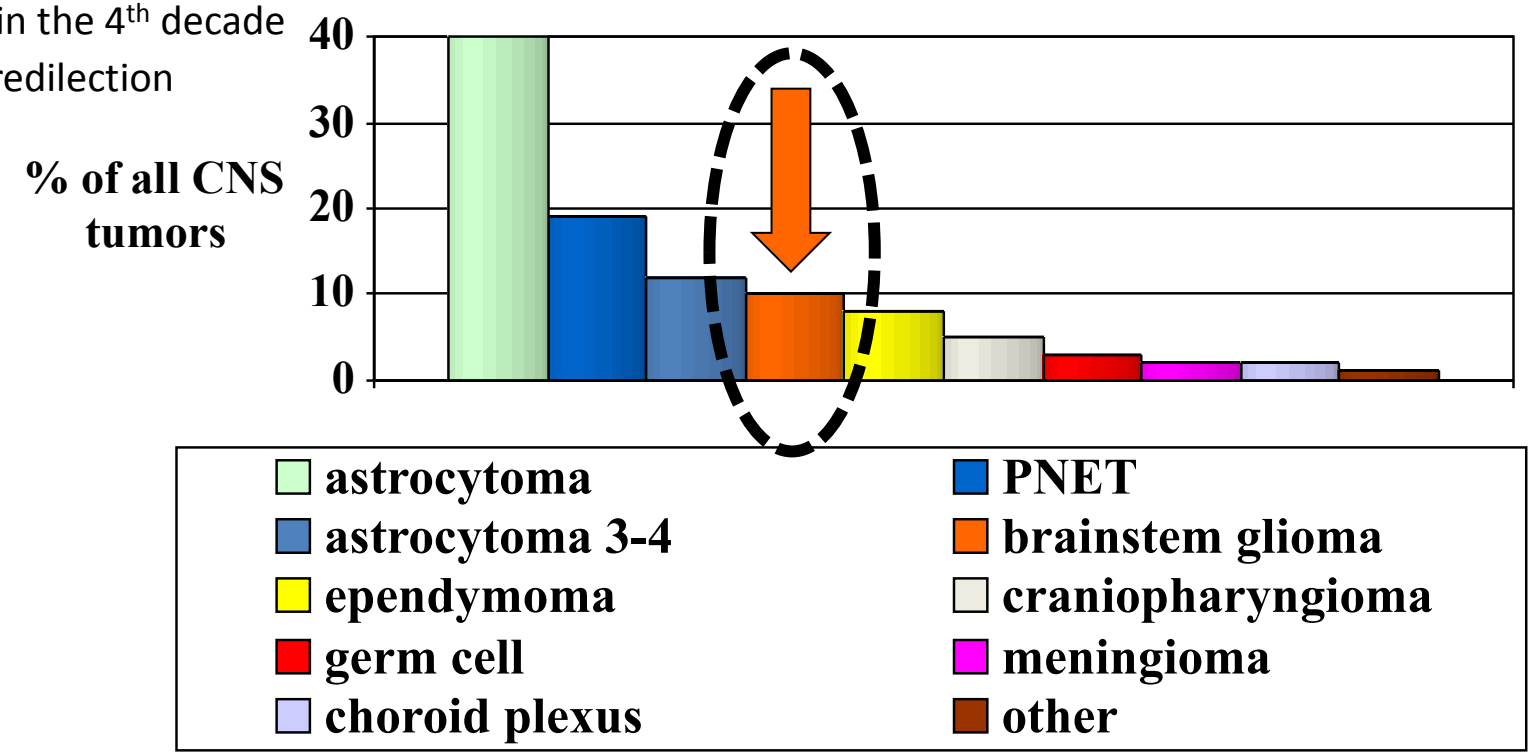
Distribution in Children and Adolescents (Age 0-19 Years) of Primary Brain and CNS Tumors by site

Neuro-Oncology
19(S5), 1–88, 2017 | doi:10.1093/neuonc/nox158

CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014

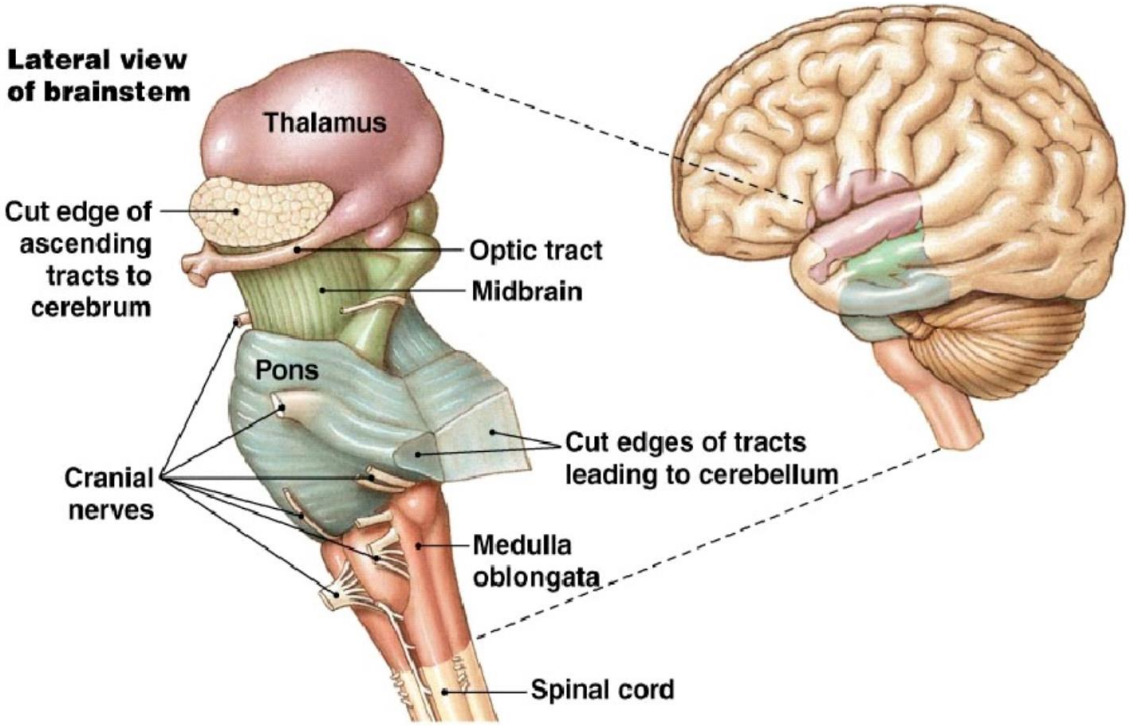
Epidemiology

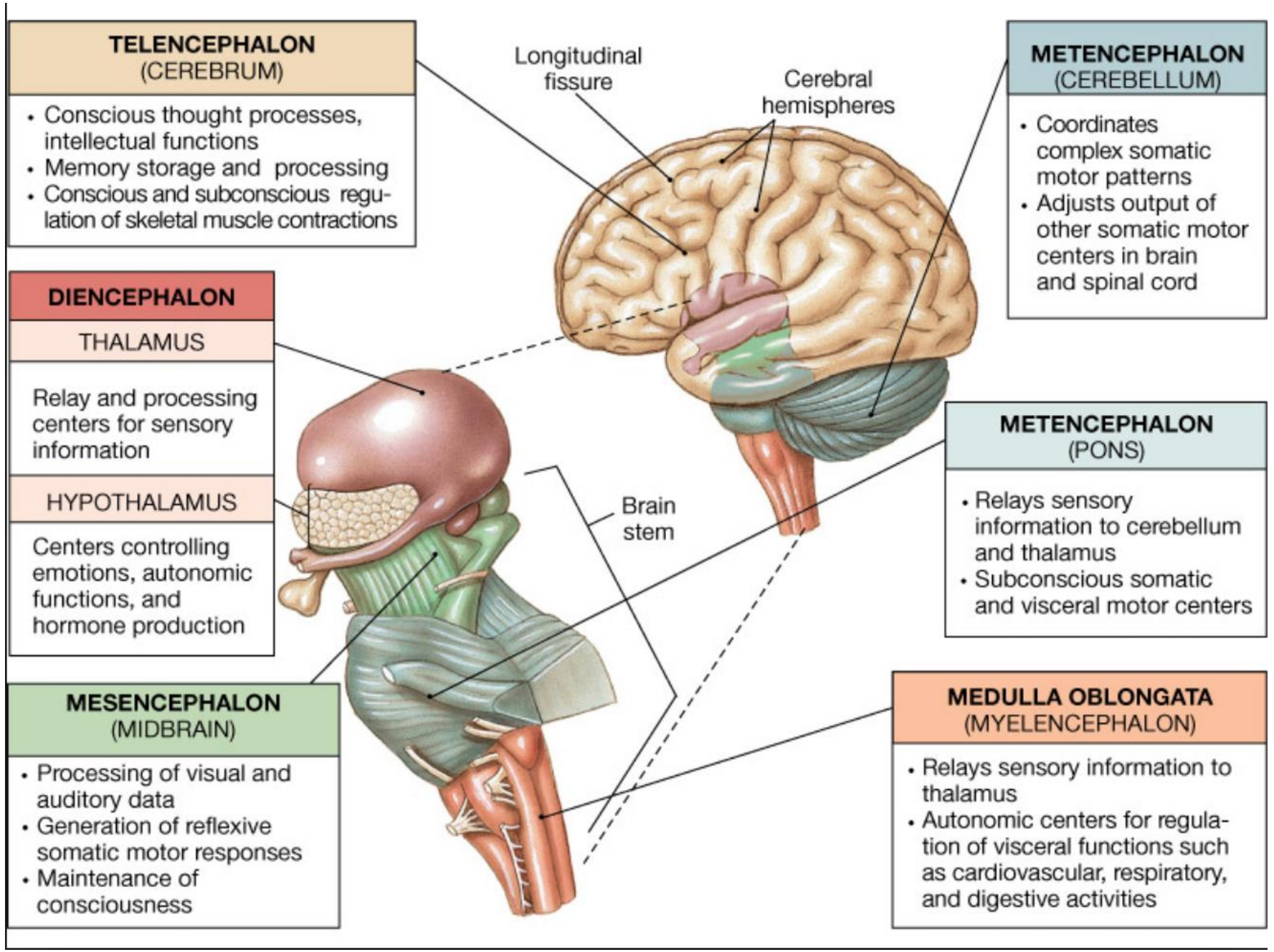
- When looking at the entire population brainstem tumors account for 1.6% of all tumors and 3.8% of all malignant tumors (CBTRUS 2010-2014)
- Represents 10 % of all brain tumors in the pediatric population
- 15-20% of posterior fossa tumors
- 80% Pontine location (In kids ~75% from brain stem tumors relate to the old entity DIPG)
- 150-200 new cases/year in North America
- Midbrain and medulla account for minority
- Occur in the first decade (more in the second half of it)
- Second peak in the 4th decade
- Slight male predilection



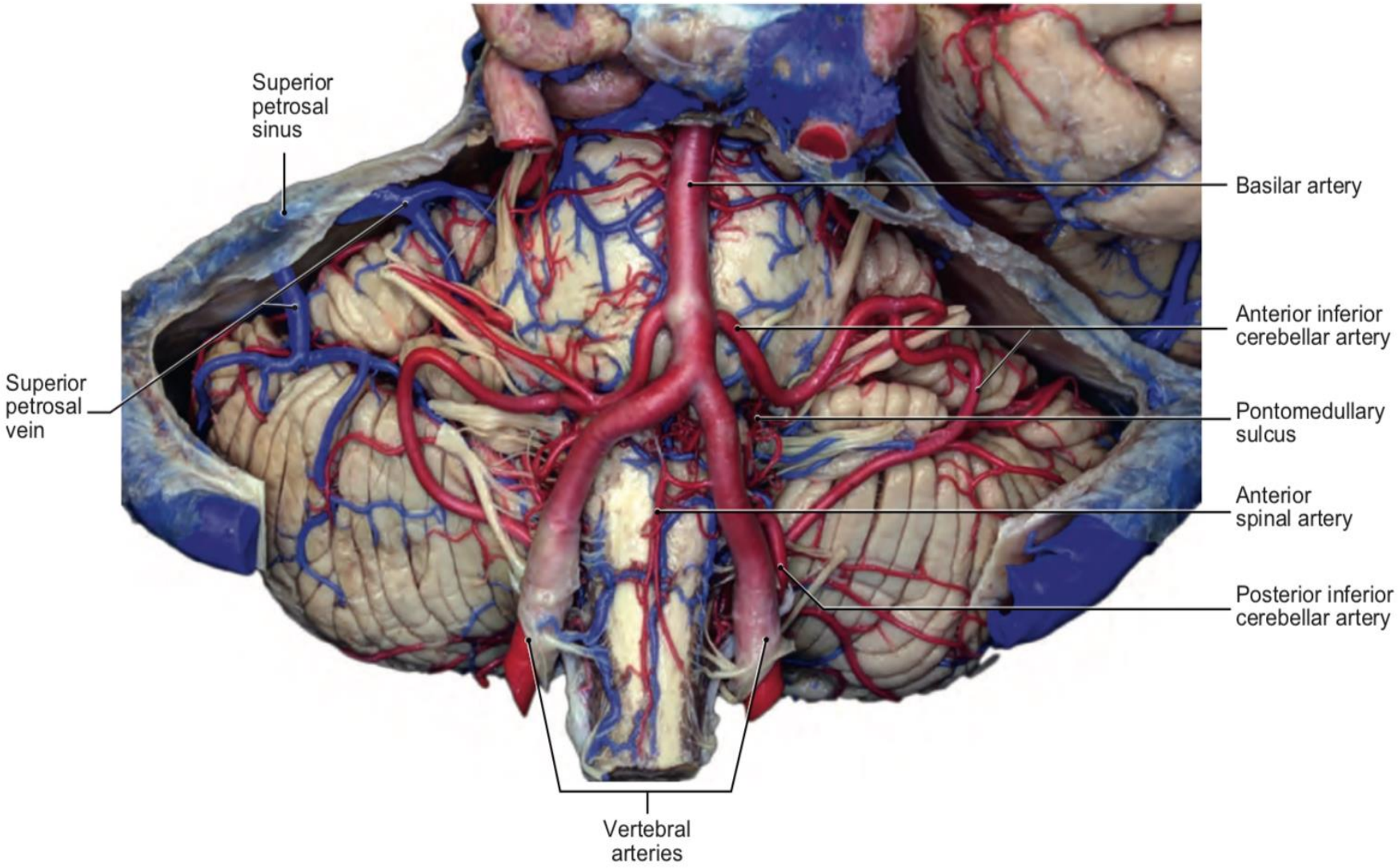
Few words on Anatomy

- Brainstem comprises the **midbrain, pons and medulla**
- Smallest part of the encephalon
- 6 cm by 3.5 cm wide
- 1/5 volume of the entire brain
- Highly complex neural circuitry (anatomically and functionally)




TELENCEPHALON
(CEREBRUM)
• Conscious thought processes, intellectual functions
• Memory storage and processing
• Conscious and subconscious regulation of skeletal muscle contractions
Longitudinal fissure
Cerebral hemispheres
METENCEPHALON
(CEREBELLUM)
• Coordinates complex somatic motor patterns
• Adjusts output of other somatic motor centers in brain and spinal cord
DIENCEPHALON
THALAMUS
Relay and processing centers for sensory information
HYPOTHALAMUS
Centers controlling emotions, autonomic functions, and hormone production
Brain stem
METENCEPHALON
(PONS)
• Relays sensory information to cerebellum and thalamus
• Subconscious somatic and visceral motor centers
MESENCEPHALON
(MIDBRAIN)
• Processing of visual and auditory data
• Generation of reflexive somatic motor responses
• Maintenance of consciousness
MEDULLA OBLONGATA
(MYELENCEPHALON)
• Relays sensory information to thalamus
• Autonomic centers for regulation of visceral functions such as cardiovascular, respiratory, and digestive activities

Very complex neurovascular anatomy

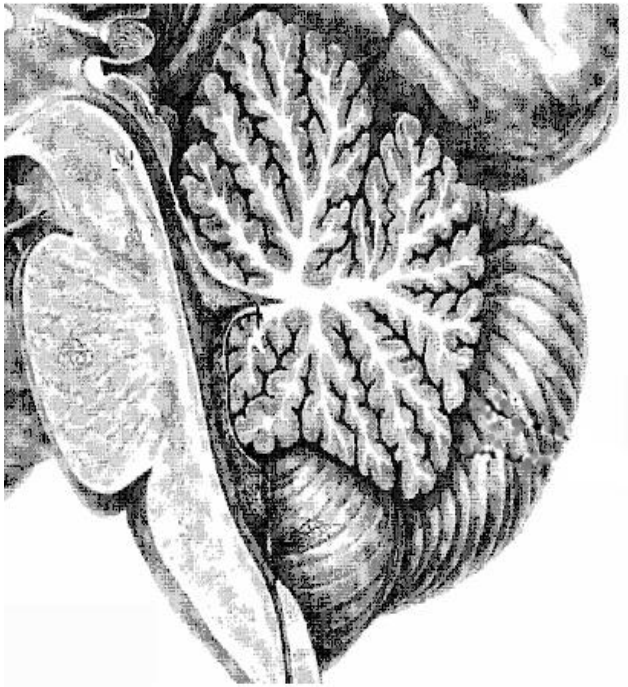


History of brainstem surgery

- Bailey 1930
  - "Until some effective treatment other than surgery is devised gliomas of the brainstem will be hopeless problems for treatment"
- Matson, 1969
  - "the location of these tumors in itself obviates the possibility of surgical removal"
  - "regardless of specific histology they must all be classified as malignant tumors, since their location in itself renders them inoperable"

    Matson DD: Neurosurgery of Infancy and Childhood, 2nd Ed. Springfield, Charles Thomas, 1969, pp.469-477.

    No distinction between different parts of the brainstem



History of brainstem surgery

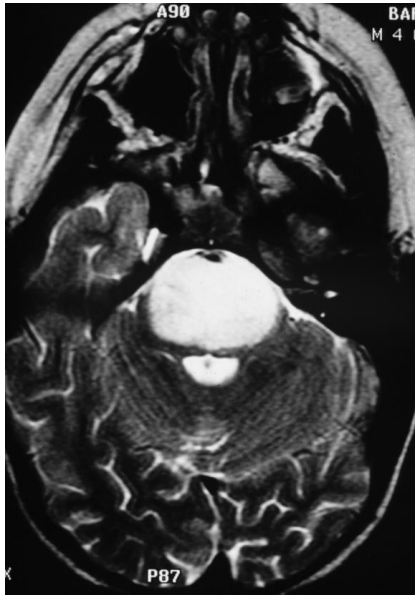
- Mean survival in these early studies
  - 4 to 15 months
  - *Matson* then "should any patient with a clinical diagnosis of brainstem glioma still be alive as long as 18 months after diagnosis, with or without x-ray treatment, reinvestigation and probably surgical exploration is indicated as some other lesion is probably present"

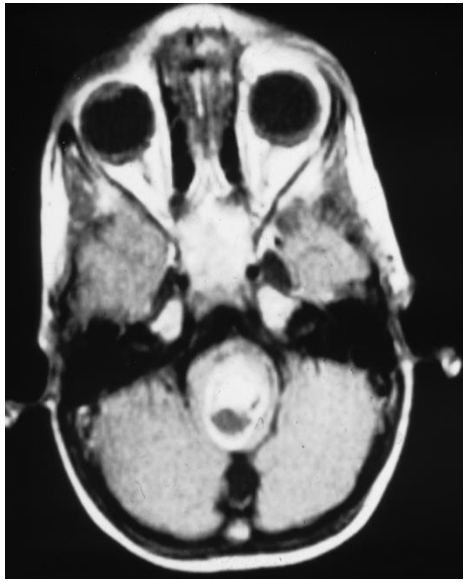
History of brainstem surgery

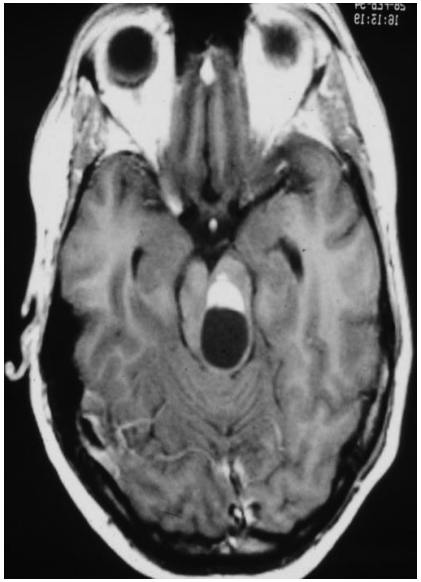
- First introduced by *Alvisi* in 1962, then *Pool* in 1968.
- It was not until the advent of CT scans (1978) and MRI (1985) that these lesions were refined.
  - *Hoffman* et al, 1980
  - *Epstein* et al, 1986

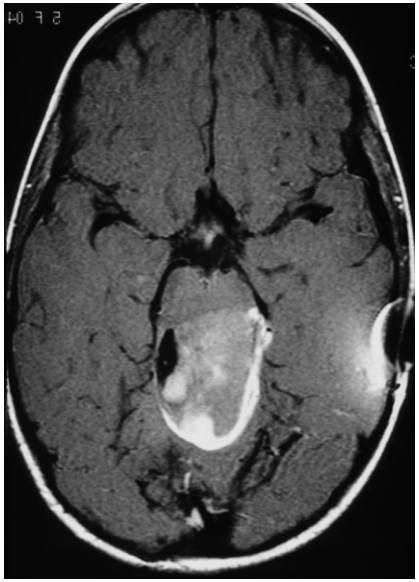
Brainstem Tumors

Classification and Surgical Options





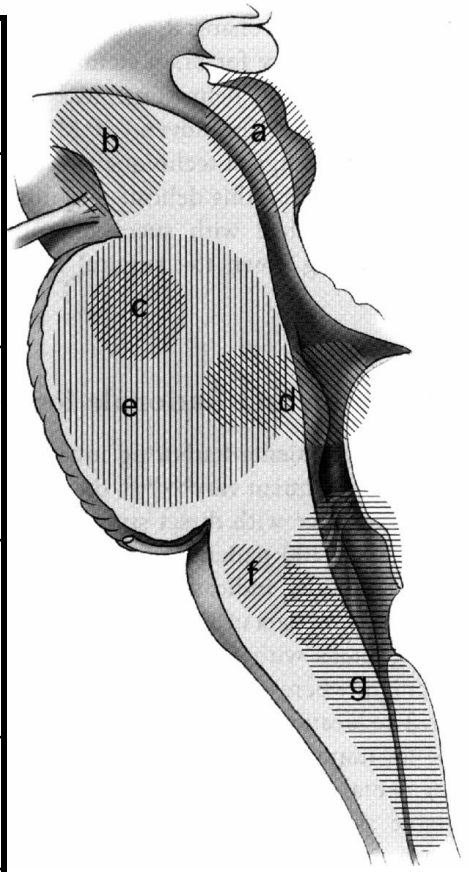




Not all brainstem tumors are alike…..

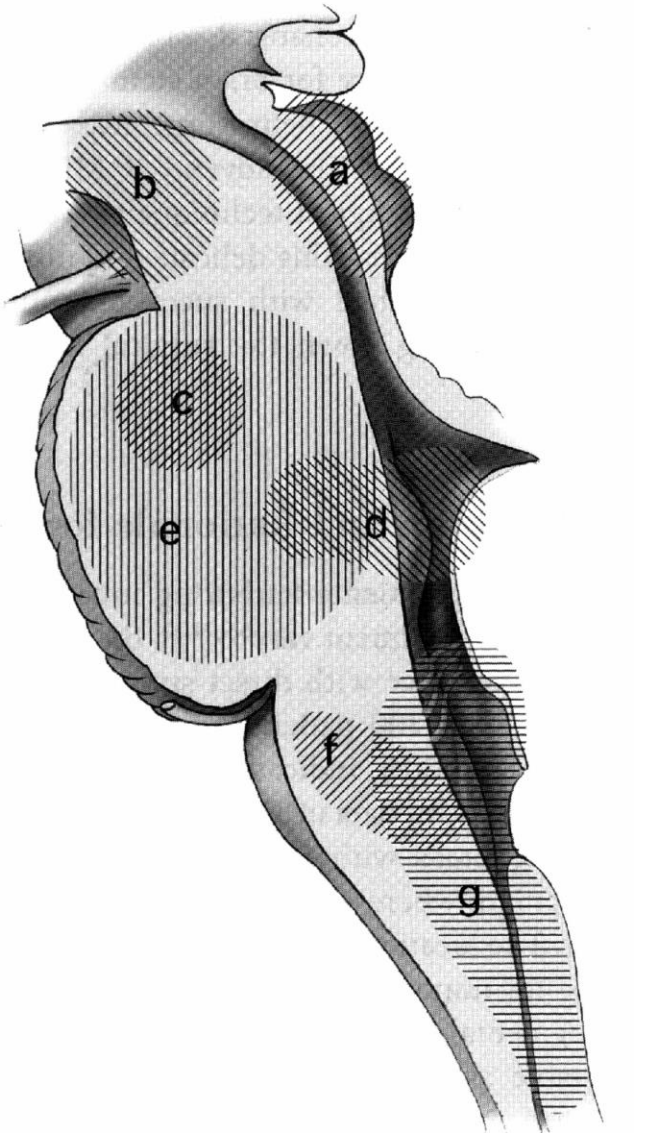
Classification System for Brainstem Tumors

Authors	Classification Scheme
Epstein, 1985	Intrinsic Exophytic Disseminated
Epstein,1986	Diffuse Focal Cervicomedullary
Fischbein, 1996	Midbrain (diffuse, focal, tectal) Pons (diffuse, focal) Medulla
Albright, 1996	Focal (midbrain, pons, medulla) Diffuse
Choux, 1999	Type 1: intrinsic tumor, diffuse Type 2: intrinsic tumor, focal Type 3: exophytic tumor, dorsal or lateral Type 4: cervicomedullary tumor



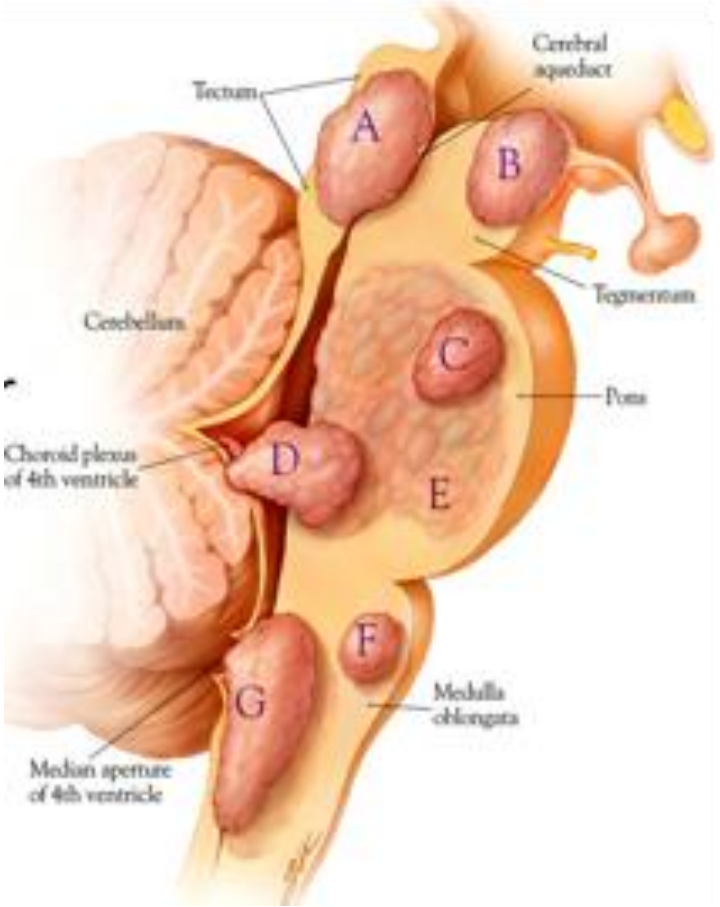
Classification System

- **Classification system based on MRI** (*Barkovich*, 1991)
  - Location
    - Midbrain, pons, medulla
  - Focality
    - Diffuse or focal
  - Direction and extent of growth
  - Degree of brainstem enlargement
  - Evidence of hydrocephalus
  - Hemorrhage or necrosis



Clinical Presentation - Characteristic Signs & Symptoms

- Malignant tumor
  - Diffuse midline glioma, K27M mutant
    - Includes the old term – "DIPG", which is the prototypical tumor describing brainstem tumors
    - High grade gliomas
  - High Grade Gliomas (non K27M mutant)
  - Embryonal tumors, C19MC-altered or not (PNETS is old term not for use)
  - Lymphoma
  - Metastases
- Benign or focal tumors
  - Location
  - Hydrocephalus



When classifications meet

- Barkovich and others designed the anatomic and radiographic classification of brainstem tumors

- WHO classification gave histology classification
- Brainstem tumors tend to be low grade tumors (that are located in a bad location), WHO II

So for years, the best solution was the exophytic tumor, low grade astrocytoma, which was easy to reach …

New era of Molecular and Genetics

- In 2016, WHO published a supplement that lead to integrating molecular and genetics into the known histological classification from 2007

- For brainstem tumors the main change is with the deletion of DIPG, and the use of new group called “Diffuse midline glioma, H3 K27M–mutant”

What are *"Diffuse midline glioma, K27M mutant"*?

- Histone H3 K27M mutations are found in **80% of the tumors used to called DIPG (diffuse pontine gliomas)**
- They are also found in other midline HGGs arising in the thalamus, cerebellum or spinal cord.
- **About 75% of histone H3 mutations occur in *H3F3A*, encoding the H3.3** isoform, and 20 – 25% of mutations occur in *HIST1H3B* or rarely *HIST1H3A/C*, encoding H3.1
- *ACVR1* mutations almost always occur concurrently with a HIST1H3B K27M mutation in diffuse pontine gliomas that present at less than 5 years of age. While H3.1 K27M mutations are also found in thalamic HGGs, *ACVR1* mutations have only been identified in diffuse pontine gliomas. Hence, molecular subtyping can reveal today the origin of the tumor
- **For patients harboring the K27M mutation the prognosis is less favorable**

Clinical signs and parameters

Diffuse tumors:

- Duration of symptoms is short
  - Less than 3 months
- Deficits
  - Cranial nerve deficit 71-85%
    - Cranial nerves V, VI, VII, IX, X
  - Cerebellar ataxia 24-87%
  - Pyramidal tracts 43-80%
    - Motor, hyperreflexia, or sensory
- Obstructive hydrocephalus
  - More common for the focal benign tumors
  - 20-55%

Focal tumors:

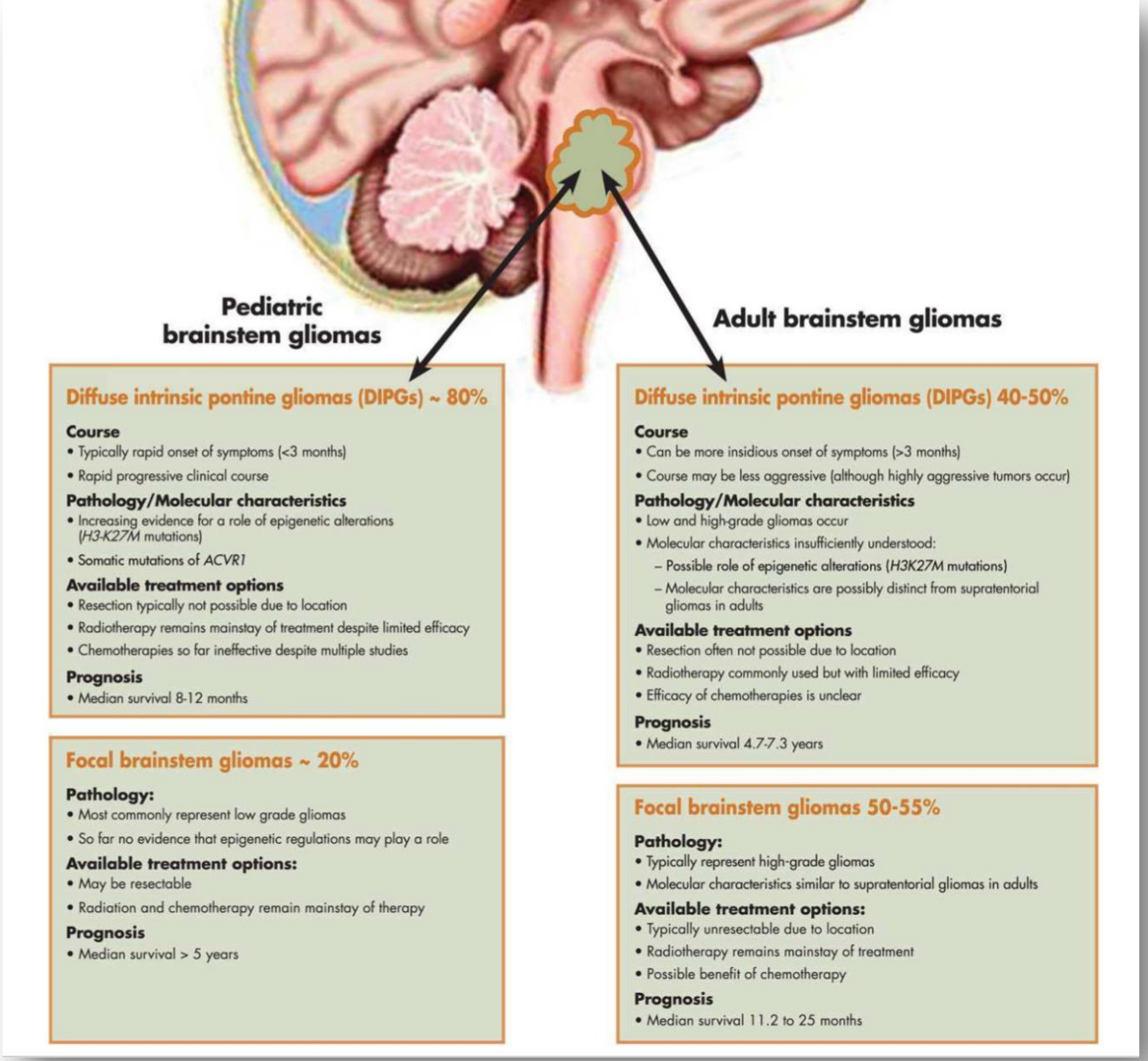
- Raised Intracranial Pressure
  - Headaches, vomiting, lethargy
- Focal deficits
  - Cranial Nerve
    - Upper (CN III-VII)
    - Lower (CN IX-XII)
  - Pyramidal Tracts
  - Syndromes
- Duration of symptoms
  - Long prodrome
  - Failure to thrive
  - Extensive medical evaluation

Imaging

MRI is the imaging modality and gold standard

- Multiplanar technique, with the sagittal plane the preferred image
- MRI devoid of artifacts
- High resolution
- New Sequences
  - DTI, MRS

- Malignant Tumors
  - Diffuse Midline Glioma
    - T1: isointense or slightly hypointense
    - T2: hyperintense
    - Gadolinium: Late in course or post treatment
  - Medulla and Midbrain account for relatively few malignant tumors

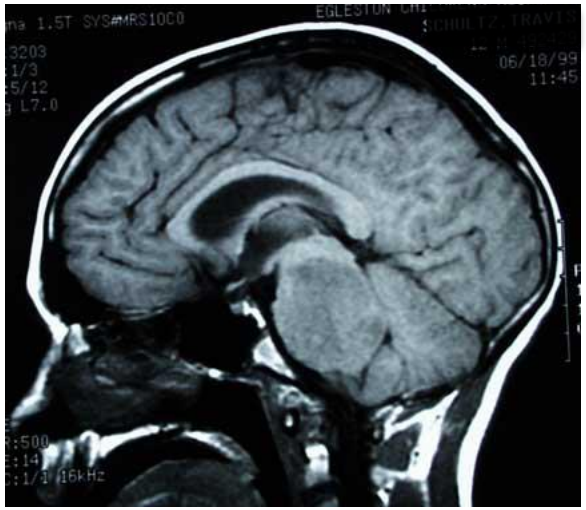


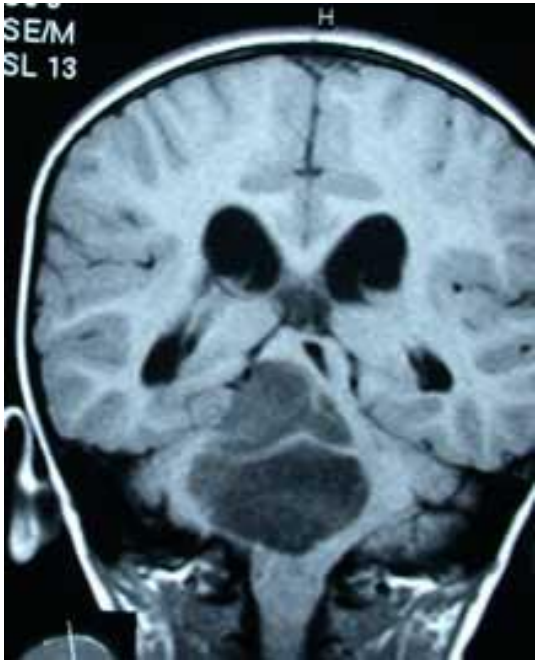
Review Article

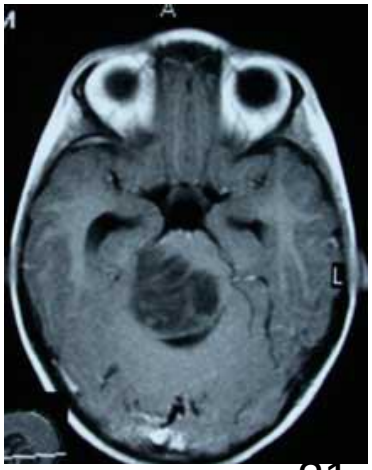
Adult Brainstem Gliomas

Sylvia C. Eisele, MD; and David A. Reardon, MD

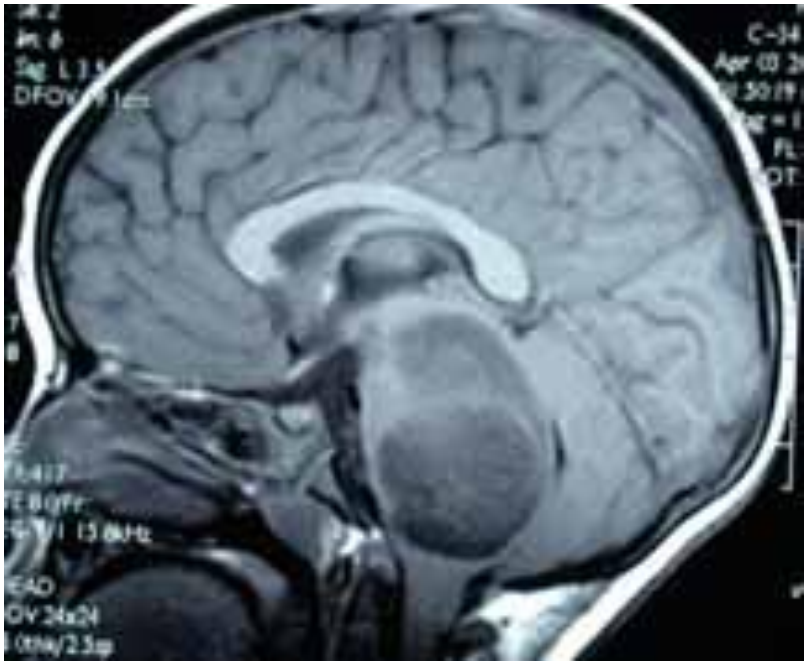
Diffuse Infiltrative Midline Gliomas

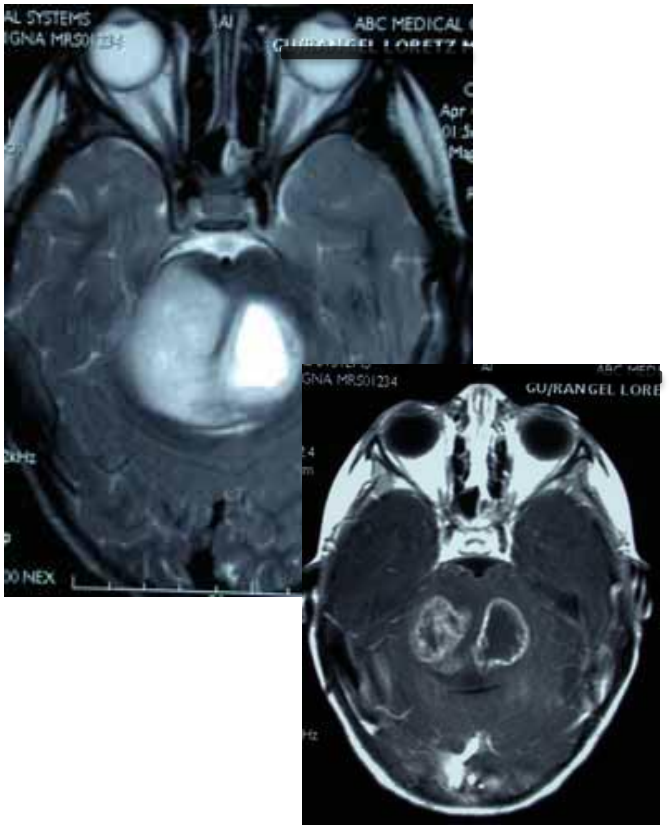




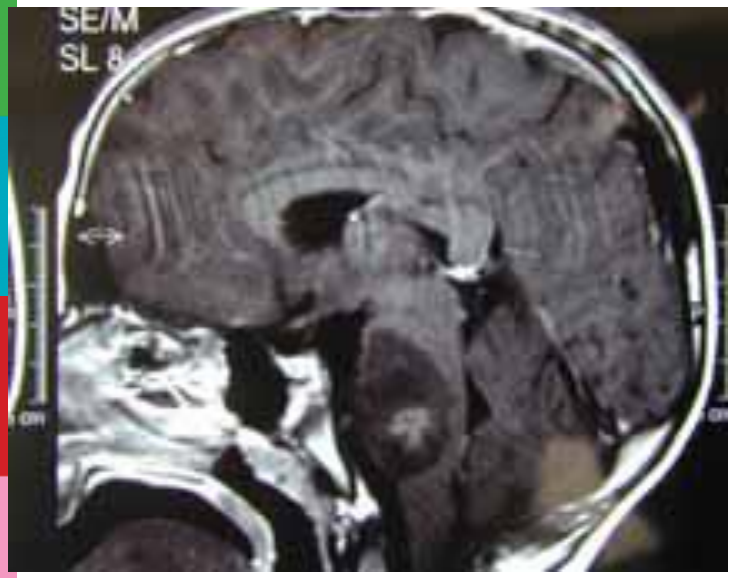


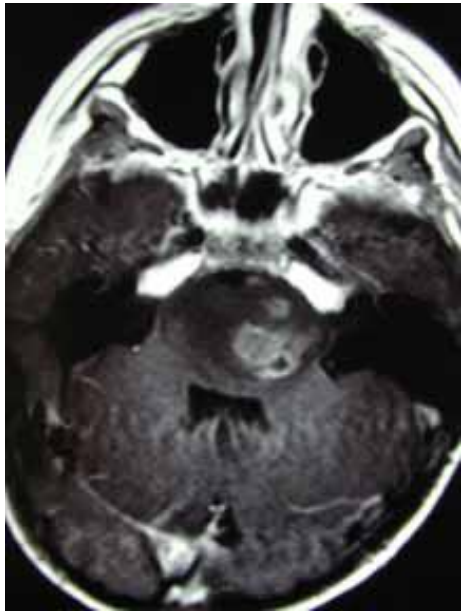
Diffuse Midline Glioma

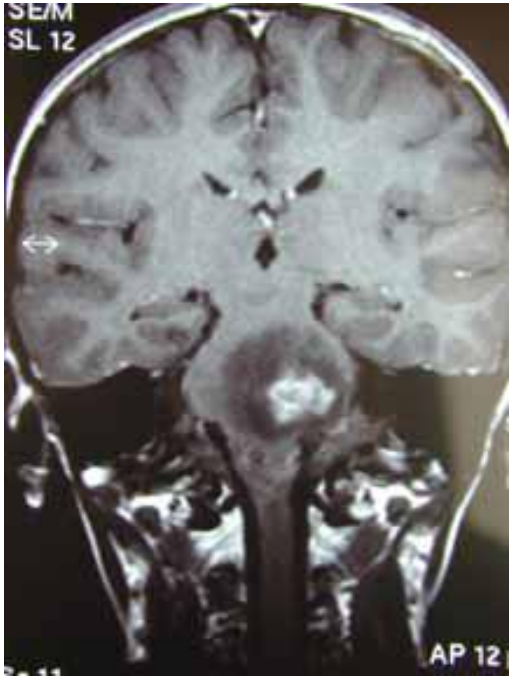




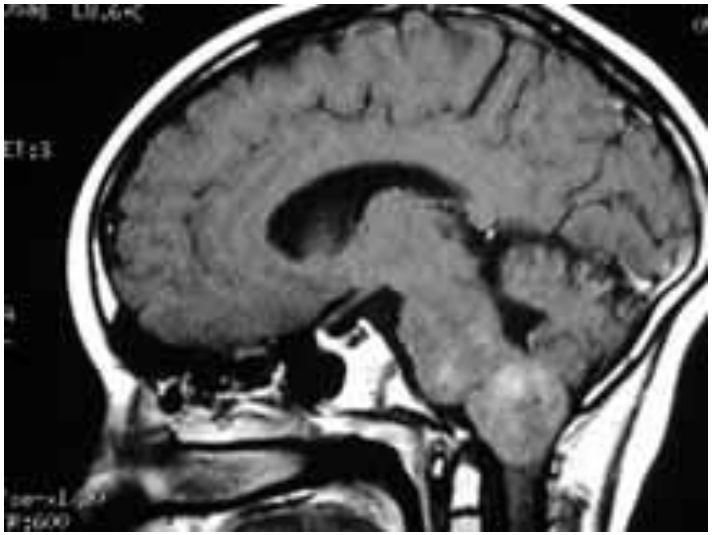
Diffuse Midline Glioma

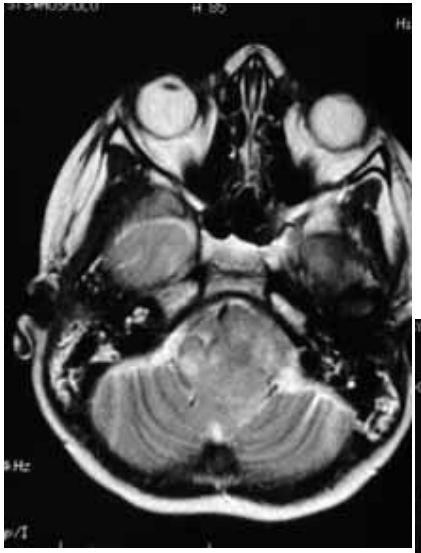


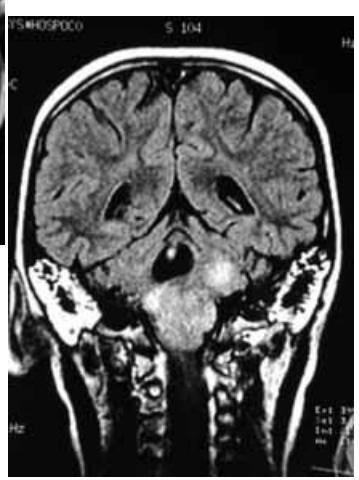




Diffuse Midline Glioma
(Medullary Extension)

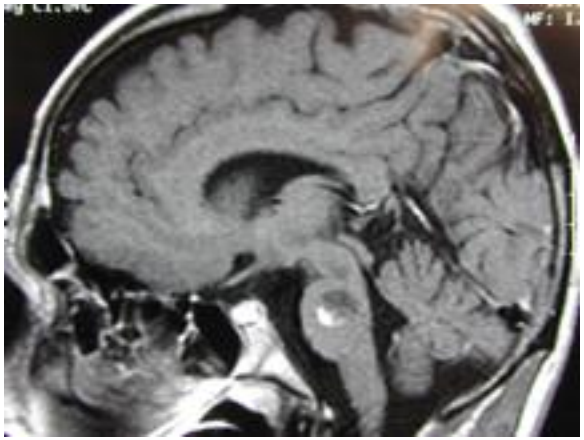


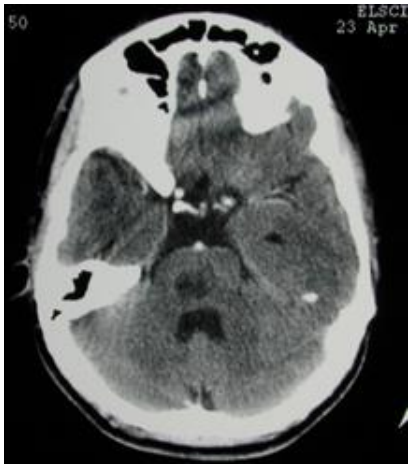


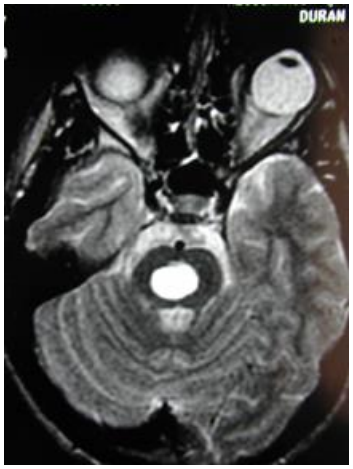


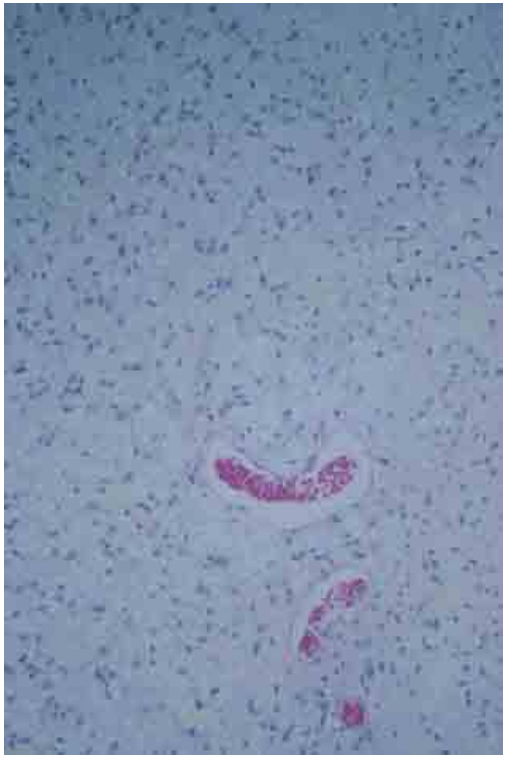
Focal Benign Brainstem Tumors:

Juvenile Pilocytic Astrocytoma

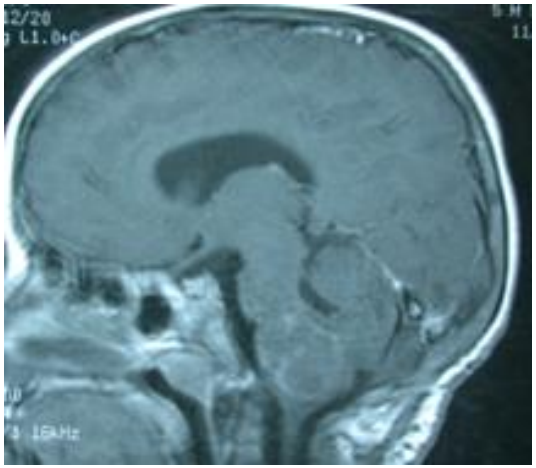


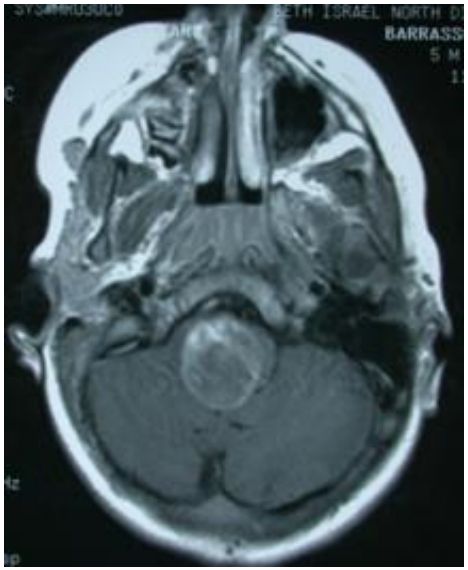


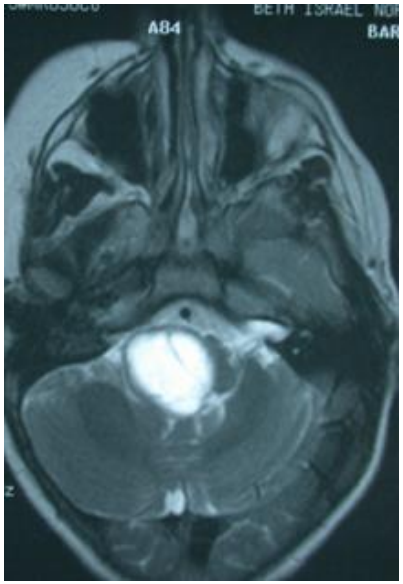


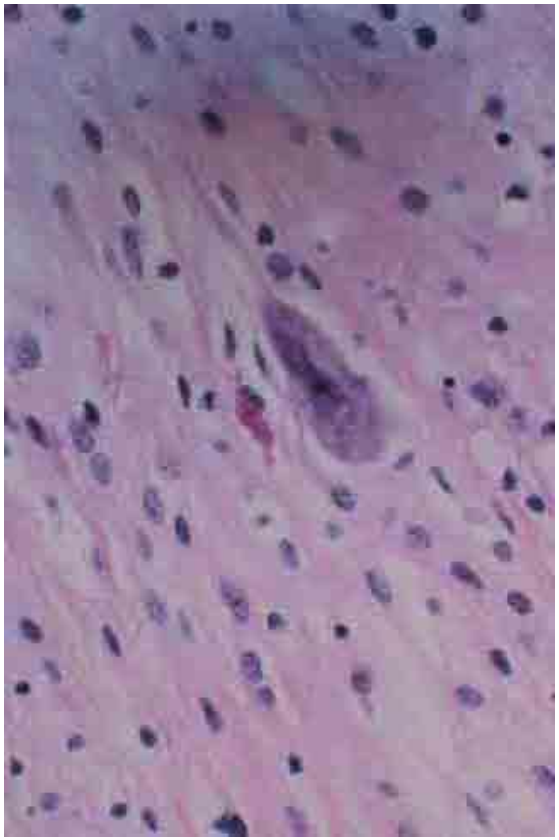


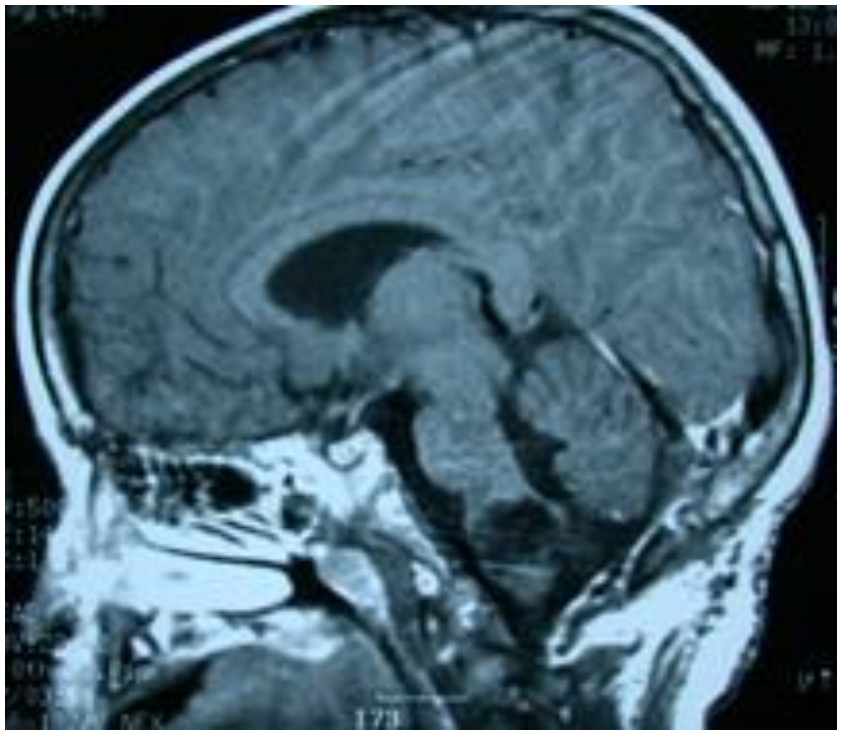
Focal Medullary Ganglioglioma

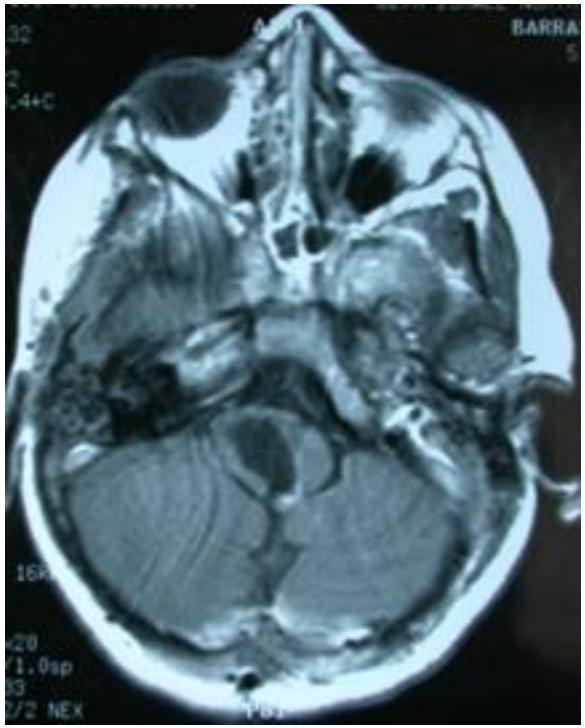












No new deficits

Management for Brainstem Tumors

- **Hydrocephalus** – Consider treating first!
  - Endoscopic Third Ventriculostomy
  - Shunt diversionary procedure
- **Diffuse Midline Tumors**
  - Need for biopsy? (currently advocate only if part of trial)
  - Can the tumor be resected (e.g., Thalamopeduncular tumors)
  - Adjuvant therapy
- **Focal Tumors**
  - Surgery
    - Biopsy
    - Radical Resection
      - Risks versus Benefits
    - Surgical Technology
  - Adjuvant Therapy
    - Radiotherapy
    - Chemotherapy

Diffuse Midline Gliomas

- Surgery has no role in the current management for this tumor, yet the need for biopsy is advocated by many
  - Histology: high grade vs. low grade
  - Molecular subtyping – **H3 K27M** mutation?
- Radiation Therapy

Philipp Kickingereder, MD*
Peter Willeit, MD‡§
Thorsten Simon, MD‖
Maximilian I. Ruge, MD*

Diagnostic Value and Safety of Stereotactic Biopsy for Brainstem Tumors: A Systematic Review and Meta-analysis of 1480 Cases

Radiotherapy

- Conventional therapy
  - 54 Gy (2cm margin) in 30 fractions over 6 weeks
  - Once daily
- Hypofractionated Radiotherapy
  - 39 Gy in 13 fractions (will be considered in cases with limited life expectancy, e.g. large diffuse tumor)
- Hyperfractionated Radiotherapy
  - Twice daily to 66, 70.2 and 75.6 Gy
    - Toxicity
    - Steroid dependence

No substantial improvement in tumor control or survival, there is no support that hyper fractionated RT benefit long term adverse effects

Radiotherapy

- Brachytherapy
  - Iodine-125 implants (Chuba et al, 1998)
  - 27 children permanent implants
    - 10 patients with brainstem tumors
      - 8 patients with pontine gliomas
      - No complications
      - Results: pending

Chemotherapy for Brainstem Gliomas

- Benefit of chemotherapy is very questionable since most tumors will harbor K27M mutation, which shows low MGMT hypermethyletion, that leads to lack of efficacy for Temozolomide
- High-dose myeloablative chemo- therapy with autologous stem-cell rescue (ASCR) has also been explored, but the role of this approach in the treatment of pediatric high-grade gliomas remains unproven. Although can benefit if GTR achieved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CrossMark

TOPIC REVIEW

Pediatric high-grade glioma: current molecular landscape and therapeutic approaches

Steve Braunstein[1] · David Raleigh[1] · Ranjit Bindra[2] · Sabine Mueller[3] · Daphne Haas-Kogan[4]

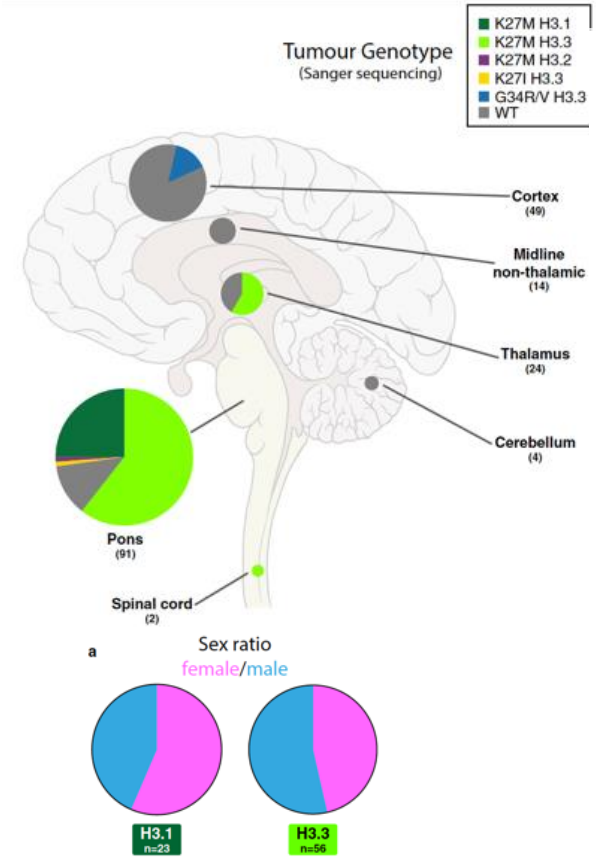
Chemotherapy for Brainstem Gliomas

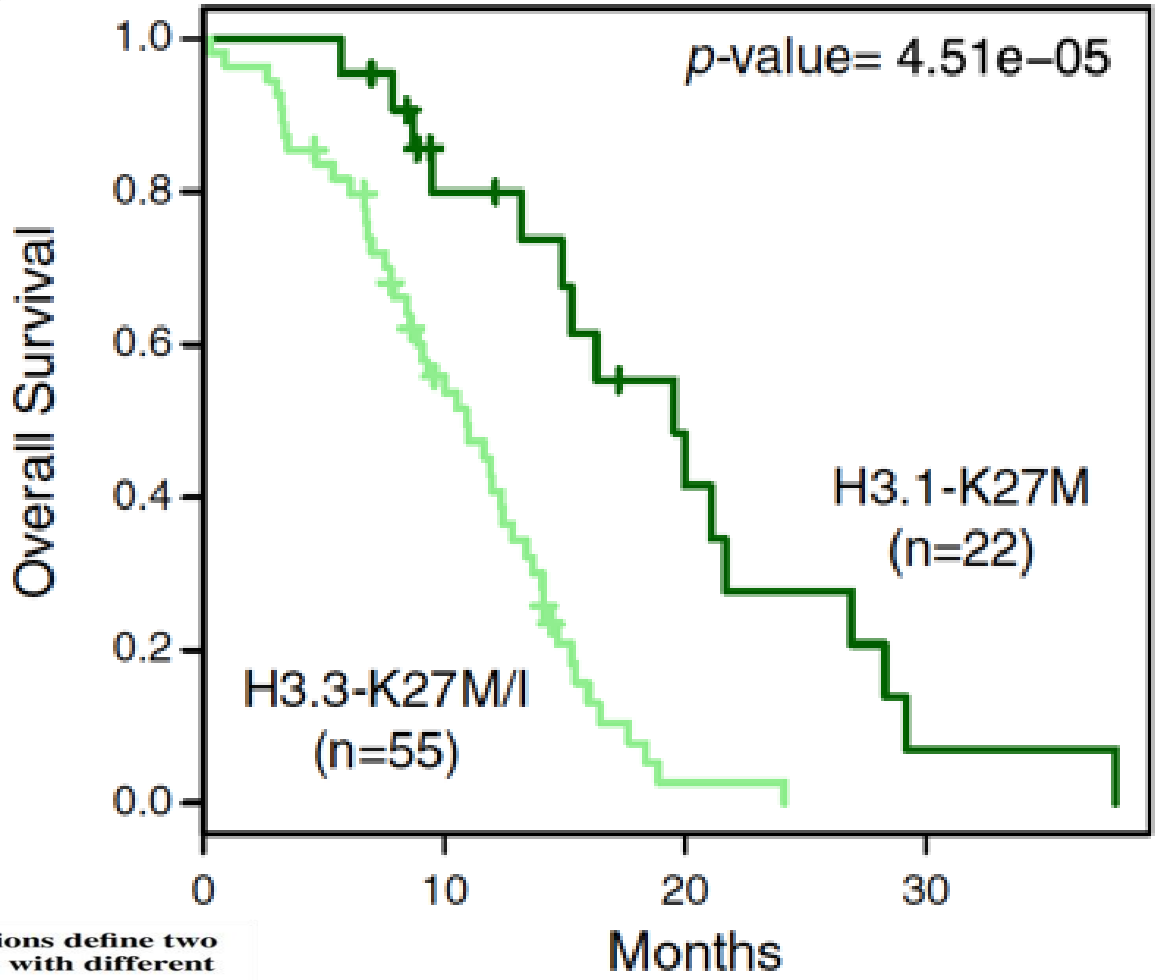
- Several protocols for chemotherapy
  - Single agents used include:
    - Cyclophosphamide, ifosfamide, PCNU, cisplatin, carboplatin, iproplatin, AZQ, thiotepa, VP-16, topetecan, temodar
  - Multiagent therapy:
    - 8-in-1, MOPP, Iphosphamide VP-16 Mesna, cisplatin Ara-C VP-16
  - High dose with autologous rescue:
    - Busulphan thiotepa, thiotepa VP-16 BCNU

Molecular and immunologic therapy

- Always look for the kinase inhibitor option
- These drugs were found to improve overall survival in patients with BRAFV600E-mutant cancers
- ~10% of pHGG harbor this mutation

Diffuse Midline Gliomas Survival





Histone *H3F3A* and *HIST1H3B* K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes

David Castel[1,2] · Cathy Philippe[1] · Raphaël Calmon[3] · Ludivine Le Dret[1] · Nathalène Truffaux[1] · Nathalie Boddaert[3] · Mélanie Pagès[7] · Kathryn R. Taylor[4] · Patrick Saulnier[5] · Ludovic Lacroix[5] · Alan Mackay[4] · Chris Jones[4] · Christian Sainte-Rose[6] · Thomas Blauwblomme[6] · Felipe Andreiuolo[7] · Stephanie Puget[6] · Jacques Grill[1,2] · Pascale Varlet[7] · Marie-Anne Debily[1,8]

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Current Open Protocols

Study of Suberoylanilide Hydroxamic Acid (SAHA) With Temsirolimus in Children With Diffuse Intrinsic Pon Glioma (DIPG)

Condition: Diffuse Intrinsic Pontine Glioma
Interventions: Drug: Vorinostat; Radiation: Radiation Therapy; Drug: Temsirolimus

Prolonged Exposure to Doxorubicin in Patients With Glioblastoma Multiforme and Diffuse Intrinsic Pontine

Conditions: Glioblastoma (GBM); DIPG
Intervention: Drug: Doxorubicin

Intra-arterial Chemotherapy for the Treatment of Progressive Diffuse Intrinsic Pontine Gliomas (DIPG).

Condition: Diffuse Intrinsic Pontine Glioma (DIPG)
Intervention: Drug: Melphalan hydrochloride

Trial of Panobinostat in Children With Diffuse Intrinsic Pontine Glioma

Condition: Glioma
Intervention: Drug: LBH589

Molecular Profiling for Individualized Treatment Plan for DIPG

Condition: Diffuse Intrinsic Pontine Glioma (DIPG)
Interventions: Other: Specialized tumor board recommendation; Radiation: Standard radiation thera

Molecular Analysis of Samples From Patients With Diffuse Intrinsic Pontine Glioma and Brainstem Glioma

Conditions: Diffuse Intrinsic Pontine Glioma; Brainstem Glioma
Intervention:

Study of the Combination of Crizotinib and Dasatinib in Pediatric Research Participants With Diffuse Pontin Glioma (DIPG) and High-Grade Glioma (HGG)

Conditions: Diffuse Intrinsic Pontine Glioma; High-grade Glioma
Interventions: Drug: Crizotinib; Drug: Dasatinib

Abemaciclib in Children With DIPG or Recurrent/Refractory Solid Tumors

Conditions: Diffuse Intrinsic Pontine Glioma; Brain Tumor, Recurrent; Solid Tumor, Recurrent; Neuroblastoma, Recurrent, Refractory; Ewing Sarcoma, Recurrent, Refractory; Rhabdomyosarcoma, Recurrent, Refractory; Osteosarcoma, Recurrent, Refractory; Rhabdoid Tumor, Recurrent, Refractory
Intervention: Drug: Abemaciclib

Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication

Condition: Diffuse Intrinsic Pontine Glioma
Interventions: Drug: Erlotinib; Drug: Everolimus; Drug: Dasatinib

Anti PD1 Antibody in Diffuse Intrinsic Pontine Glioma

Condition: DIPG
Intervention: Biological: MDV9300

A Phase I/II Study of Ribociclib,a CDK4/6 Inhibitor, Following Radiation Therapy

Conditions: High Grade Glioma; Diffuse Intrinsic Pontine Glioma; Bithalamic High Grade Glioma
Intervention: Drug: Ribociclib

A Phase I Study of Mebendazole for the Treatment of Pediatric Gliomas

Conditions: Pilomyxoid Astrocytoma; Pilocytic Astrocytoma; Glioma, Astrocytic; Optic Nerve Glioma; Pleomorphic Xanthoastrocytoma; Glioblastoma Multiforme; Anaplastic Astrocytoma; Gliosarcoma; Diffuse Intrinsic Pontine Glioma; DIPG; Low-grade Glioma; Brainstem Glioma
Interventions: Drug: Mebendazole; Drug: Vincristine; Drug: Carboplatin; Drug: Temozolomide; Drug: Bevacizumab; Drug: Irinotecan

Diffuse Intrinsic Pontine Glioma (DIPG) Reirradiation (ReRT)

Condition: Brain Cancer
Intervention: Radiation: Radiation Therapy

A Study of DSP-7888 in Pediatric Patients With Relapsed or Refractory High Grade Gliomas

Conditions: Glioblastoma; Diffuse Intrinsic Pontine Glioma
Intervention: Drug: DSP-7888

Pembrolizumab in Treating Younger Patients With Recurrent, Progressive, or Refractory High-Grade Gliomas or Diffuse Intrinsic Pontine Gliomas

Conditions: Diffuse Intrinsic Pontine Glioma; Malignant Glioma; Recurrent Childhood Brain Neoplasm
Interventions: Procedure: Diffusion Tensor Imaging; Procedure: Diffusion Weighted Imaging; Procedure: Dynamic Contrast-Enhanced Magnetic Resonance Imaging; Procedure: Dynamic Susceptibility Contrast-Enhanced Magnetic Resonance Imaging; Other: Laboratory Biomarker Analysis; Procedure: Magnetic Resonance Spectroscopic Imaging; Biological: Pembrolizumab; Procedure: Perfusion Magnetic Resonance Imaging

Convection-Enhanced Delivery of 124I-8H9 for Patients With Non-Progressive Diffuse Pontine Gliomas Previously Treated With External Beam Radiation Therapy

Conditions: Brain Cancer; Brain Stem Glioma
Intervention: Radiation: Radioactive iodine-labeled monoclonal antibody 8H9

Phase I Study of Mebendazole Therapy for Recurrent/Progressive Pediatric Brain Tumors

Conditions: Medulloblastoma; Astrocytoma, Grade III; Glioblastoma; Anaplastic Astrocytoma; Brain Stem Neoplasms, Malignant; Oligodendroblastoma; Anaplastic Oligodendroglioma; Malignant Glioma
Intervention: Drug: Mebendazole

Prospective Trial of Two Hypofractionated Radiotherapy Regimens Versus Conventional Radiotherapy in Diffuse Brainstem Glioma in Children

Condition: Pediatric Brain Stem Glioma
Interventions: Radiation: Hypofractionated Arm (1); Radiation: Hypofractionated Arm (2); Radiation: Conventional Arm (3)

Future Directions for Malignant Tumors

- Chemotherapy
  - New Agents
  - Local Delivery
    - Convection-enhanced Delivery into the Rat Brainstem. JNS 96:885-891, 2002.
    - Successful and Safe Perfusion of the Primate Brainstem: in vivo Magnetic Resonance Imaging of Macromolecular Distribution during Infusion. JNS 97:905-913, 2002
- Radiotherapy
  - Interstitial therapy
  - Radiosensitizers, protectors

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Local delivery methods of therapeutic agents in the treatment of diffuse intrinsic brainstem gliomas

C. Rory Goodwin, Risheng Xu, Rajiv Iyer, Eric W. Sankey, Ann Liu, Nancy Abu-Bonsrah, Rachel Sarabia-Estrada, James L. Frazier, Daniel M. Sciubba, George I. Jallo*

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Intranasal delivery

ABSTRACT

Brainstem gliomas comprise 10–20% of all pediatric central nervous system (CNS) tumors and diffuse intrinsic pontine gliomas (DIPGs) account for the majority of these lesions. DIPG is a rapidly progressive disease with almost universally fatal outcomes and a median survival less than 12 months. Current standard-of-care treatment for DIPG includes radiation therapy, but its long-term survival effects are still under debate. Clinical trials investigating the efficacy of systemic administration of various therapeutic agents have been associated with disappointing outcomes. Recent efforts have focused on improvements in chemotherapeutic agents employed and in methods of localized and targeted drug delivery. This review provides an update on current preclinical and clinical studies investigating treatment options for brainstem gliomas.

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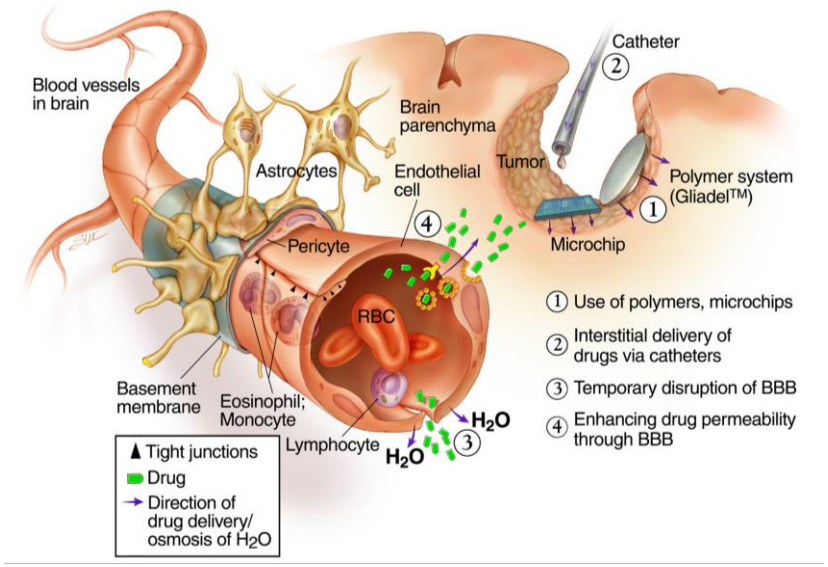
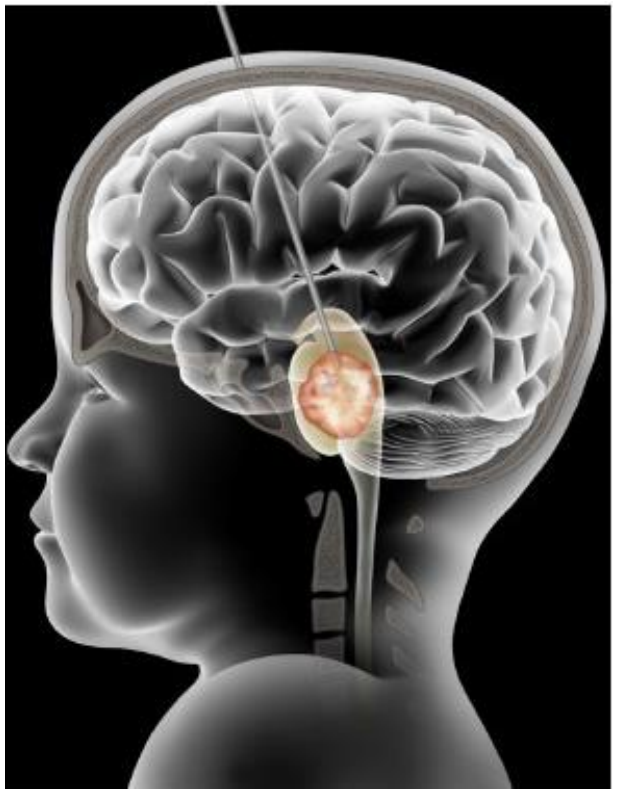
PROOF

Future Therapies for Diffuse Midline Brainstem Tumors





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PMCID: PMC5327456

Convection-Enhanced Delivery for Diffuse Intrinsic Pontine Glioma Treatment

Zhiping Zhou,[1,*] Ranjodh Singh,[2] and Mark M. Souweidane[1,3,4]

Early History for Local Delivery

J Neurosurg 99:893–898, 2003

Safety and efficacy of convection-enhanced delivery of gemcitabine or carboplatin in a malignant glioma model in rats

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Object. Convection-enhanced delivery (CED) can be used safely to perfuse regions of the central nervous system (CNS) with therapeutic agents in a manner that bypasses the blood–brain barrier (BBB). These features make CED a potentially ideal method for the distribution of potent chemotherapeutic agents with certain pharmacokinetic properties to tumors of the CNS. To determine the safety and efficacy of the CED of two chemotherapeutic agents (with properties ideal for this method of delivery) into the CNS, the authors perfused naive rats and those harboring 9L gliomas with carboplatin or gemcitabine.

Methods. Dose-escalation toxicity studies were performed by perfusing the striatum (10 μl, 24 rats) and brainstem (10 μl, 16 rats) of naive rats with carboplatin (0.1, 1, and 10 mg/ml) or gemcitabine (0.4, 4, and 40 mg/ml) via CED. Efficacy trials involved the intracranial implantation of 9L tumor cells in 20 Fischer 344 rats. The tumor and surrounding regions were perfused with 40 μl of saline (control group, four rats), 1 mg/ml of carboplatin (four rats), or 4 mg/ml of gemcitabine (four rats) 7 days after implantation. Eight rats harboring the 9L glioma were treated with the systemic administration of 60 mg/kg of carboplatin (four rats) or 150 mg/kg of gemcitabine (four rats) 7 days postimplantation. Clinical, gross, and histological analyses were used to determine toxicity and efficacy.

Toxicity occurred in rats that had received only the highest dose of the CED of carboplatin or gemcitabine. Among rats with 9L gliomas, all control and systemically treated animals died within 26 days of tumor implantation. Long-term survival (120 days) and eradication of the tumor occurred in both CED-treated groups (75% of rats in the carboplatin group and 50% of rats in the gemcitabine group). Furthermore, animals harboring the 9L glioma and treated with intratumoral CED of carboplatin or gemcitabine survived significantly longer than controls treated with intratumoral saline ($p < 0.01$) or systemic chemotherapy ($p < 0.01$).

Conclusions. The perfusion of sensitive regions of the rat brain can be accomplished without toxicity by using therapeutic concentrations of carboplatin or gemcitabine. In addition, CED of carboplatin or gemcitabine to tumors in this glioma model is safe and has potent antitumor effects. These findings indicate that similar treatment paradigms may be useful in the treatment of glial neoplasms in humans.

KEY WORDS • glioma • carboplatin • chemotherapy • gemcitabine • convection-enhanced delivery • rat

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Reprint requests:

PROLONGED CONVECTION-ENHANCED DELIVERY INTO THE RAT BRAINSTEM

OBJECTIVE: Prolonged convection-enhanced delivery was used in an attempt to achieve large volumes of distribution (V_d) in the rat brainstem. Clinical assessment and histological analysis were performed to establish the safety of this approach.

METHODS: For evaluation of V_d, 10 rats underwent stereotactic cannula placement into the brainstem. Five rats underwent a 24-hour infusion (volume of infusion [V_i], 200 μl), and 5 rats underwent a 7-day infusion (V_i, 2 ml) of fluorescein isothiocyanate-dextran. Serial brainstem sections were imaged with ultraviolet illumination, and V_d was assessed. For assessment of clinical tolerance, 30 additional rats underwent chronic infusions of an isotonic saline solution into the brainstem. Serial neurological examinations were performed, followed by histological analysis after the animals' death.

RESULTS: No animal demonstrated clinically recognized neurological deficits. Foci of organizing necrosis were limited to the site of infusion and cannula tract. V_d increased linearly with increasing V_i (range, 24.8–130.6 mm^3). Maximal cross sectional area of fluorescence and craniocaudal extent of fluorescence increased with increasing V_i. Fluorescence was detected throughout the entire brainstem beyond the compact area of highly concentrated tracer.

CONCLUSION: Prolonged convection-enhanced delivery can be applied safely in the rat brainstem with no recognized limitations of V_d and minimal histological changes beyond the site of infusion. Chronic brainstem infusions may enhance the potential application of convection-enhanced delivery for therapeutic purposes in treating diffuse pontine gliomas.

KEY WORDS: Brainstem tumor, Chronic infusion, Convection-enhanced delivery, Diffuse pontine glioma

Neurosurgery 52:388-394, 2003 DOI: 10.1227/01.NEU.0000043676.83723.8D www.neurosurgery-online.com

Studies for Local Delivery

Studies investigating delivery modalities for brainstem tumors.

Author	Delivery method	Subject	Compound
Carson et al. [43]	CED	Rat	Carboplatin
Sandberg et al. [41]	CED	Rat	Fluorescein isothiocyanate-dextran
Lonser et al. [61]	CED	Primate	Gd-bound albumin
Storm et al. [55]	CED	Primate	Carboplatin
Occhiogrosso et al. [42]	CED	Rat	Fluorescein isothiocyanate-dextran
Degen et al. [44]	CED	Rat	Carboplatin, Gemcitabine
Strege et al. [54]	CED	Primate	Carboplatin
Wu et al. [30]	CED	Rat	Carboplatin
Souweidane et al. [45]	CED	Rat	Carmustine, O6-benzylguanine
Souweidane et al. [64]	CED	Rat	IL13-PE38QQR
Lonser et al. [52]	CED	Human	IL13-PE38QQR, Glucocerbrosidase
Murad et al. [56]	CED	Primate	Gemcitabine
Hashizume et al. [60]	Intranasal	Rat	Telemorase inhibitor GRN163
Lee et al. [72]	Human neural & mesenchymal stem cells	Rat	IFN-ß, CD, 5-FC
Tange et al. [59]	ICI	Rat	Carboplatin, oxaliplatin
Thomale et al. [46]	CED	Rat	Carboplatin
Thomale et al. [52]	CED (multiple cannulas)	Rat	Carboplatin
Saito et. al. [57]	CED	Human	Nimustine hydrochloride
Yoshimura et. [48]	CED	Rat	Temozolomide
Anderson et al. [58]	CED	Human	Topotecan
Luther et. al. [87]	CED	Rat and Primate	Theragnostic ^{131}I-8H9
Sewing et. al. [49]	CED	Mouse	Carmustine
Zhou et. al. [50]	CED	Mouse	Small molecule kinase inhibitors: combinations of dasatinib, everolimus, perifosine

PROOF

Clinical Significance for Local Delivery

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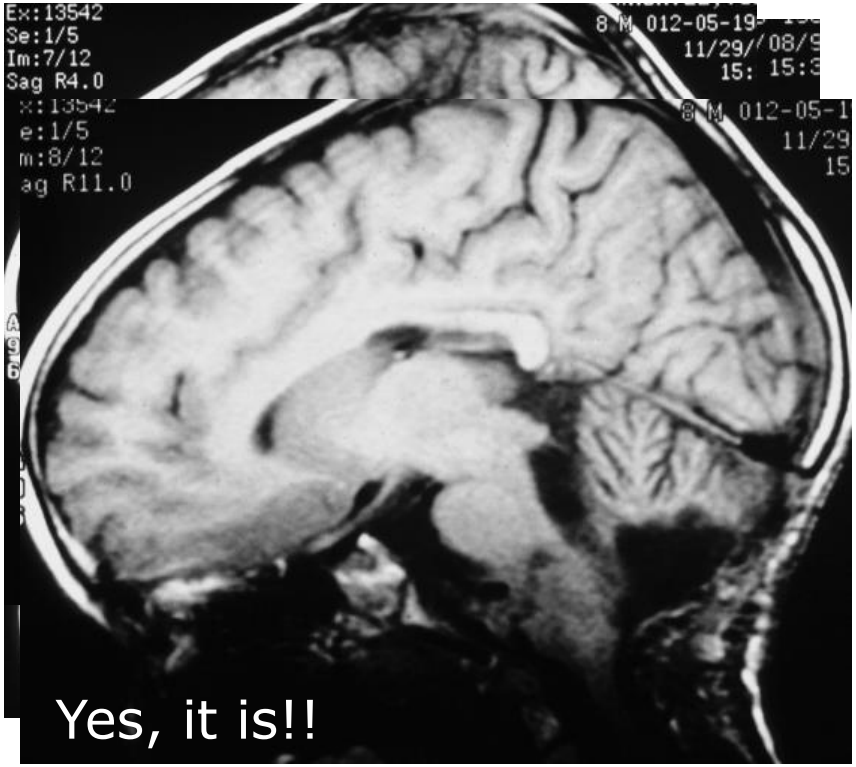
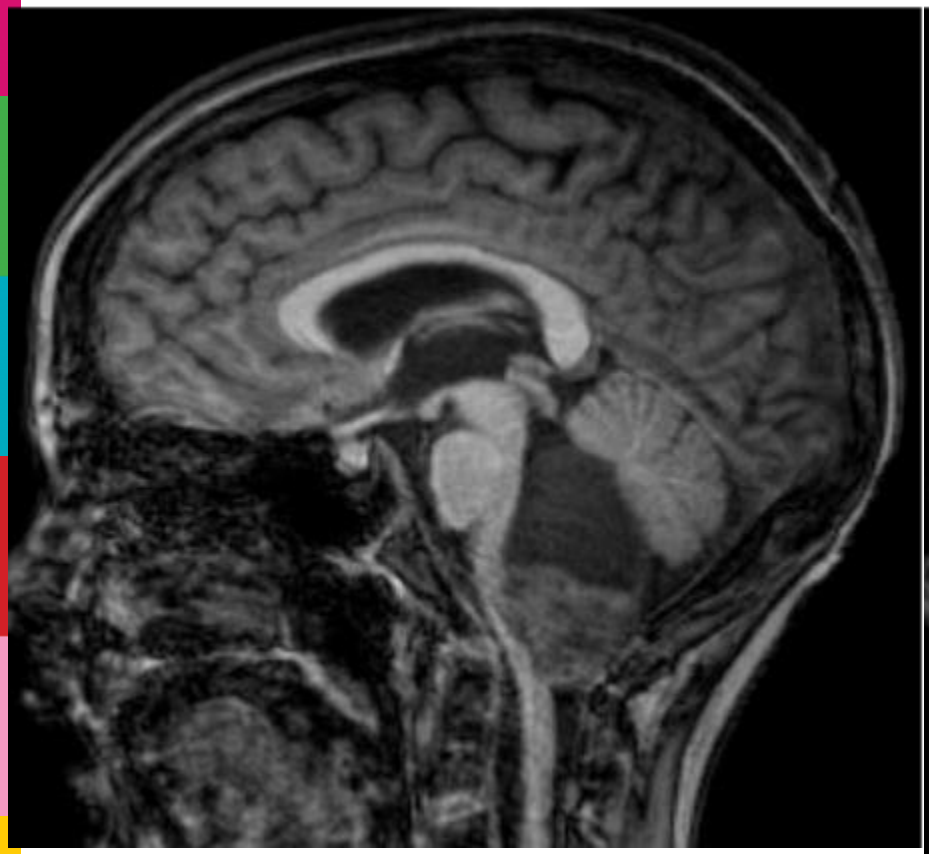
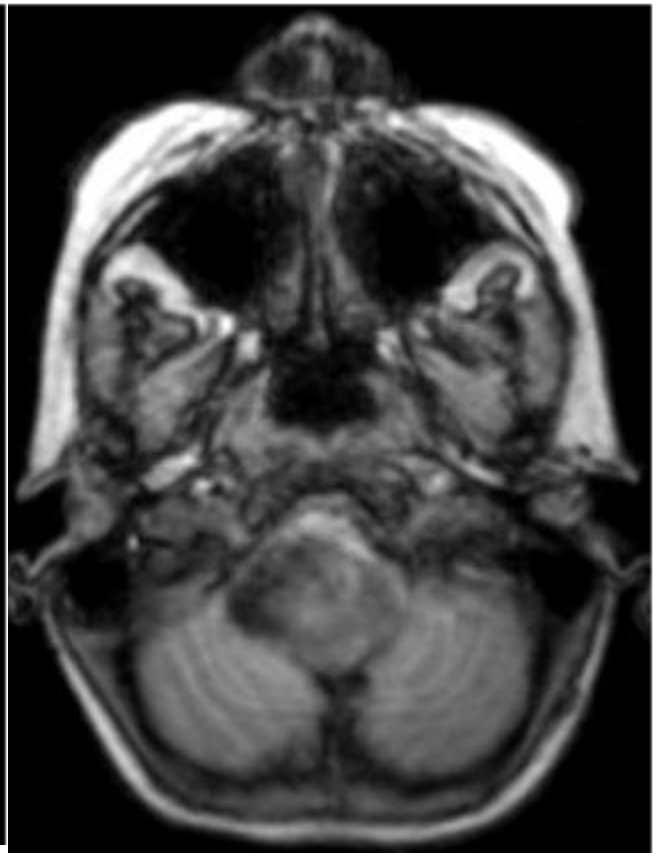
The Ultimate Focal Tumor
(Is the brainstem necessary??)

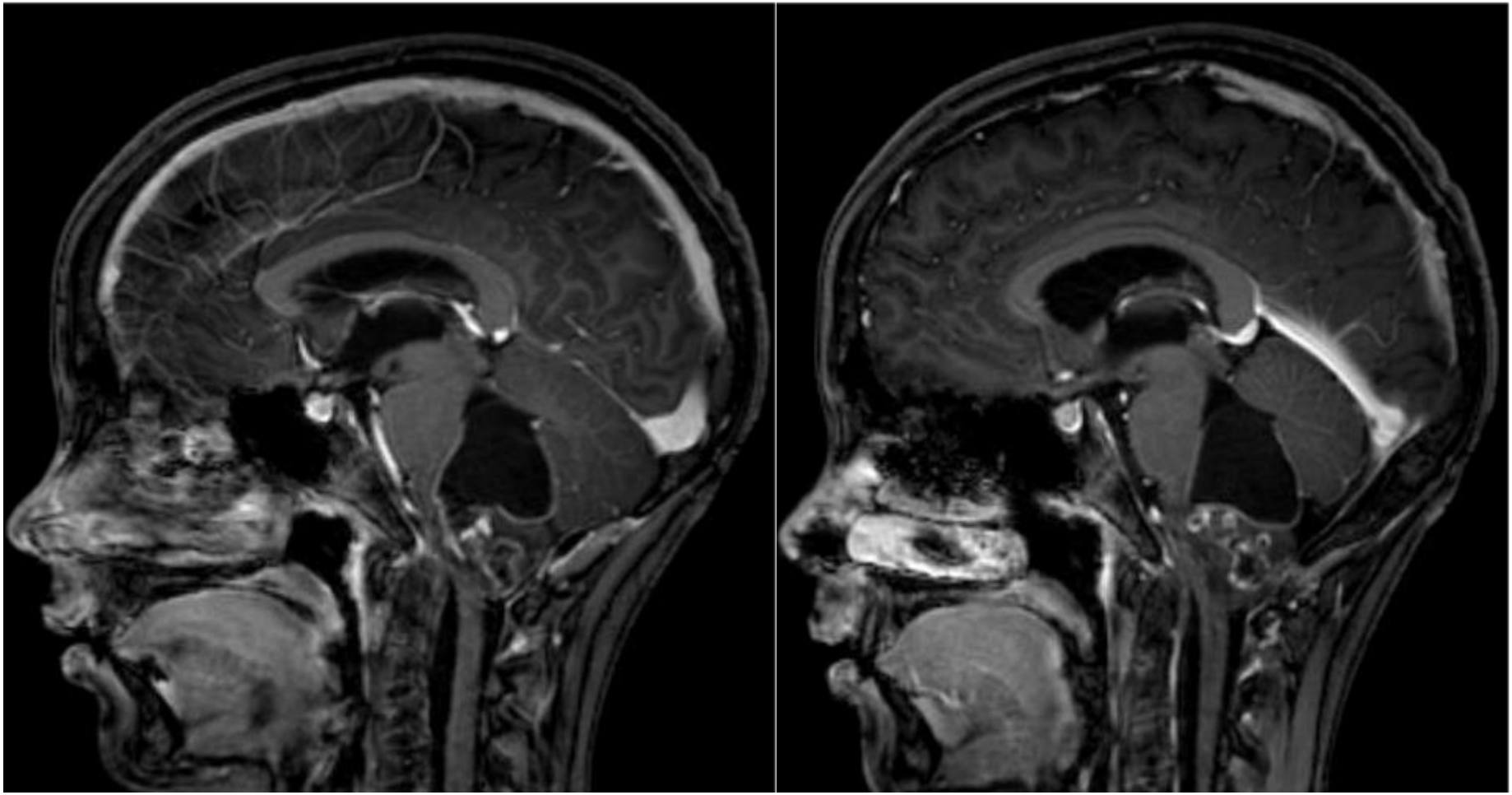


Illustrative Case

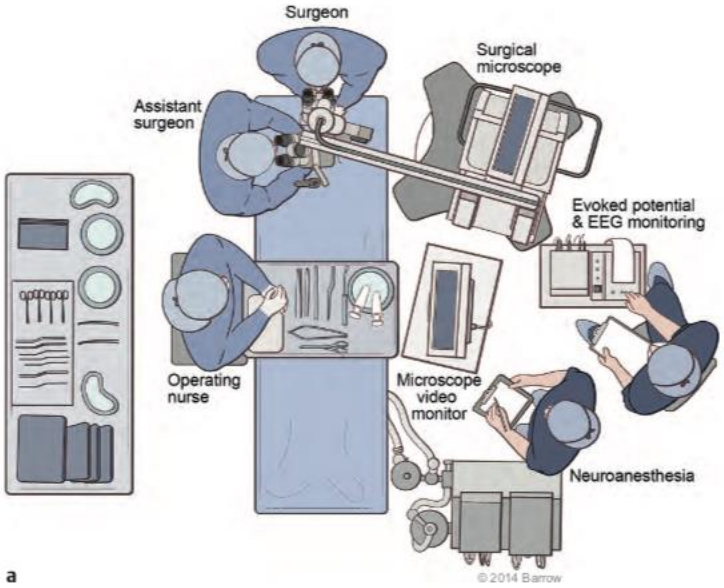
- 8 yo boy otherwise healthy
  - No past medical history
- Symptoms >12 months duration
  - Headaches,Vision problems- double vision, Swallowing and coughing difficulty







Neurophysiological Monitoring



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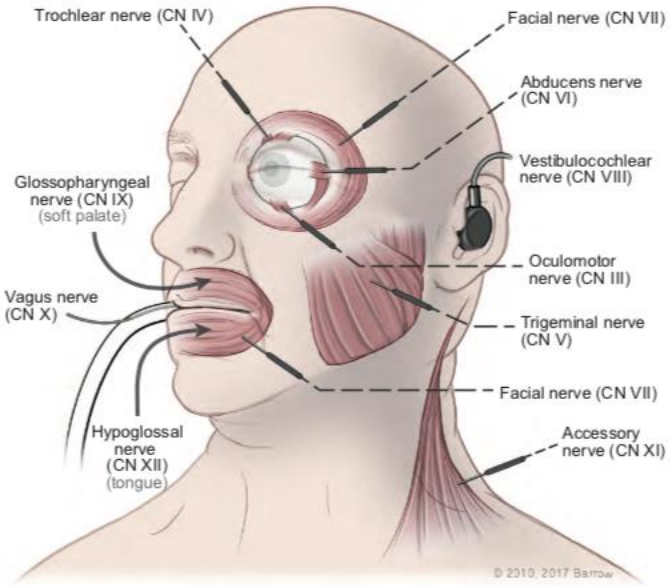
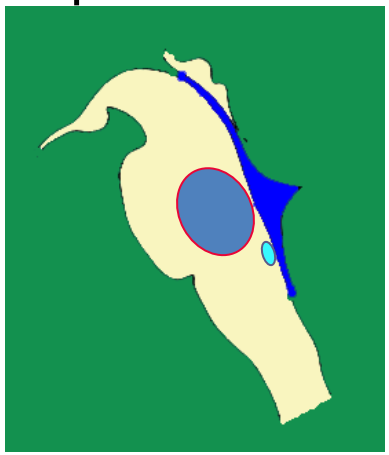


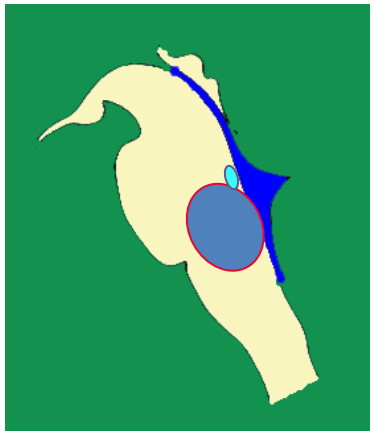
CN monitoring as well as corticospinal tracts

Anesthesiology team needs to be alert to any change in vital signs!!!

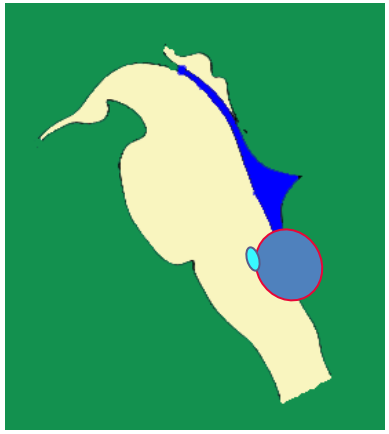
Displacement of the Cranial Nerve Nuclei



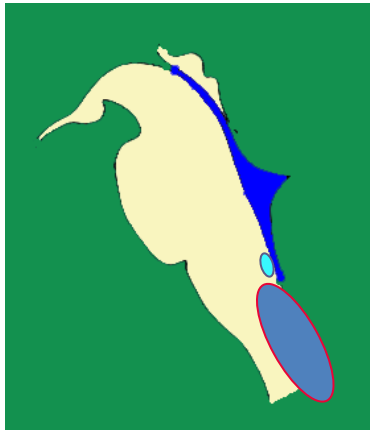
Upper Pontine Tumor



Lower Pontine Tumor

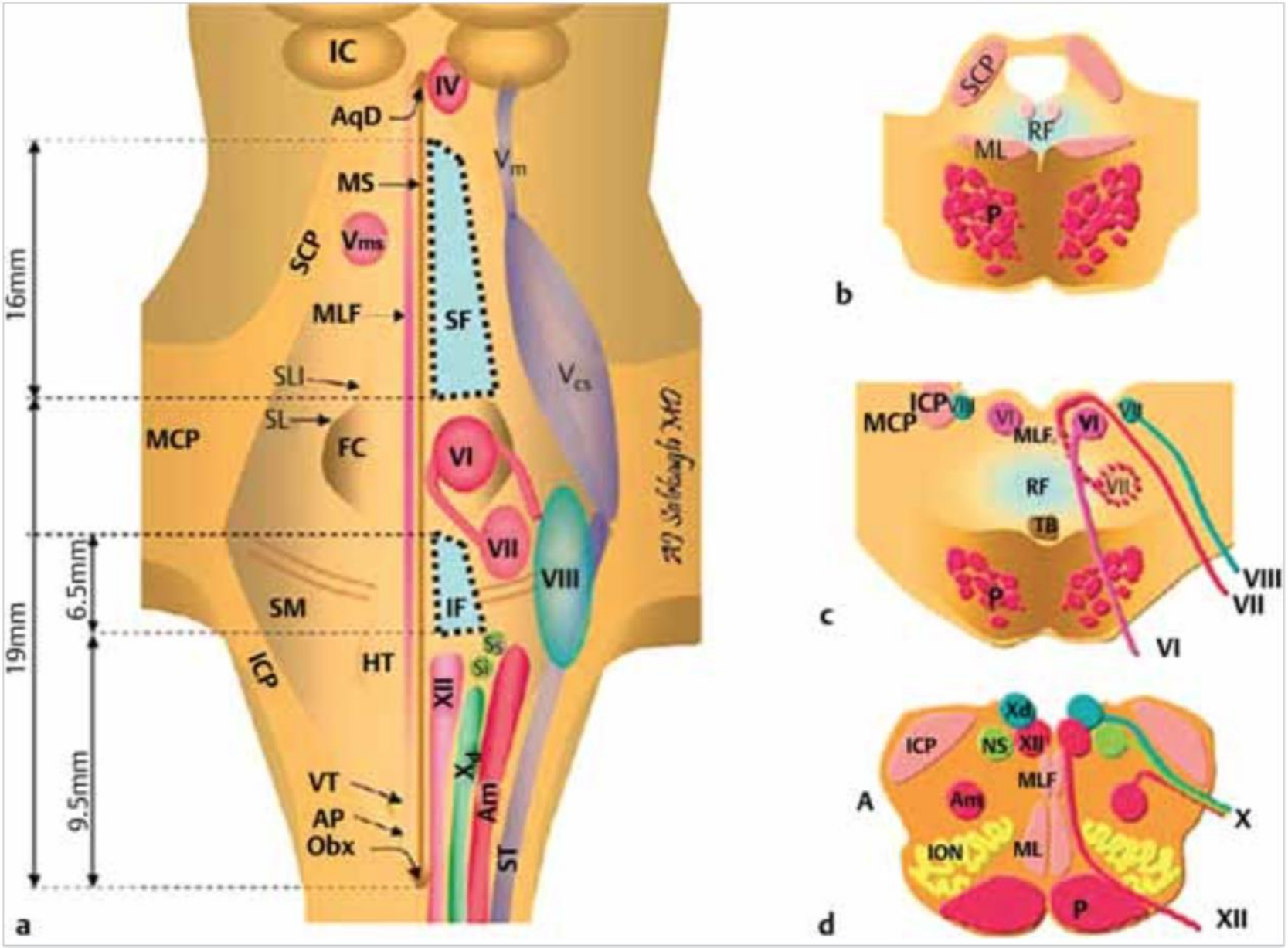


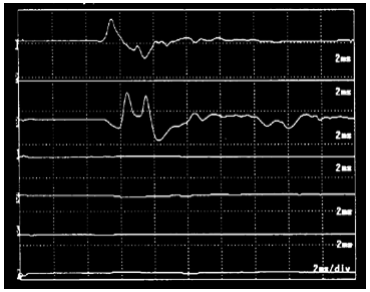
Dorsal Exophytic Tumor



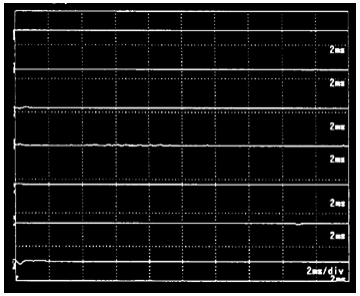
Cervicomedullary Tumor

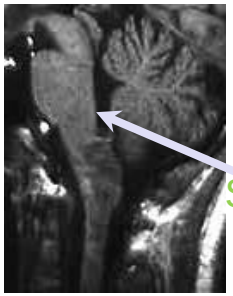
Focal Tumors: Surgical Consideration



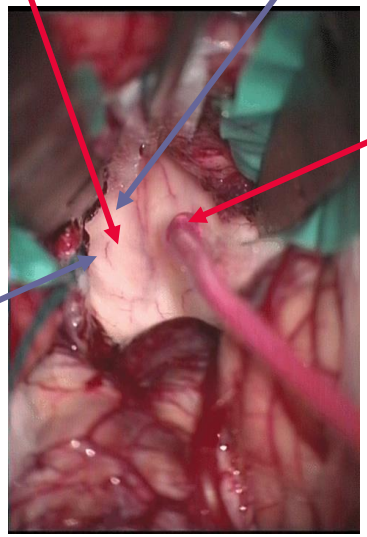


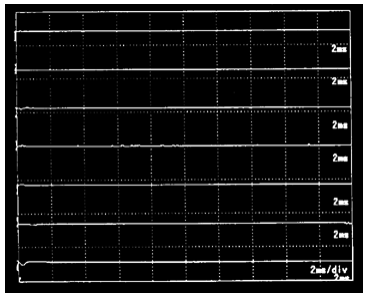
Lt.upper VII
Rt.upper VII
Lt.lower VII
Rt.lower VII
Lt.XII
Rt.XII
Bil.IX/X

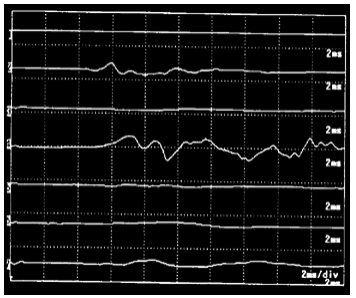




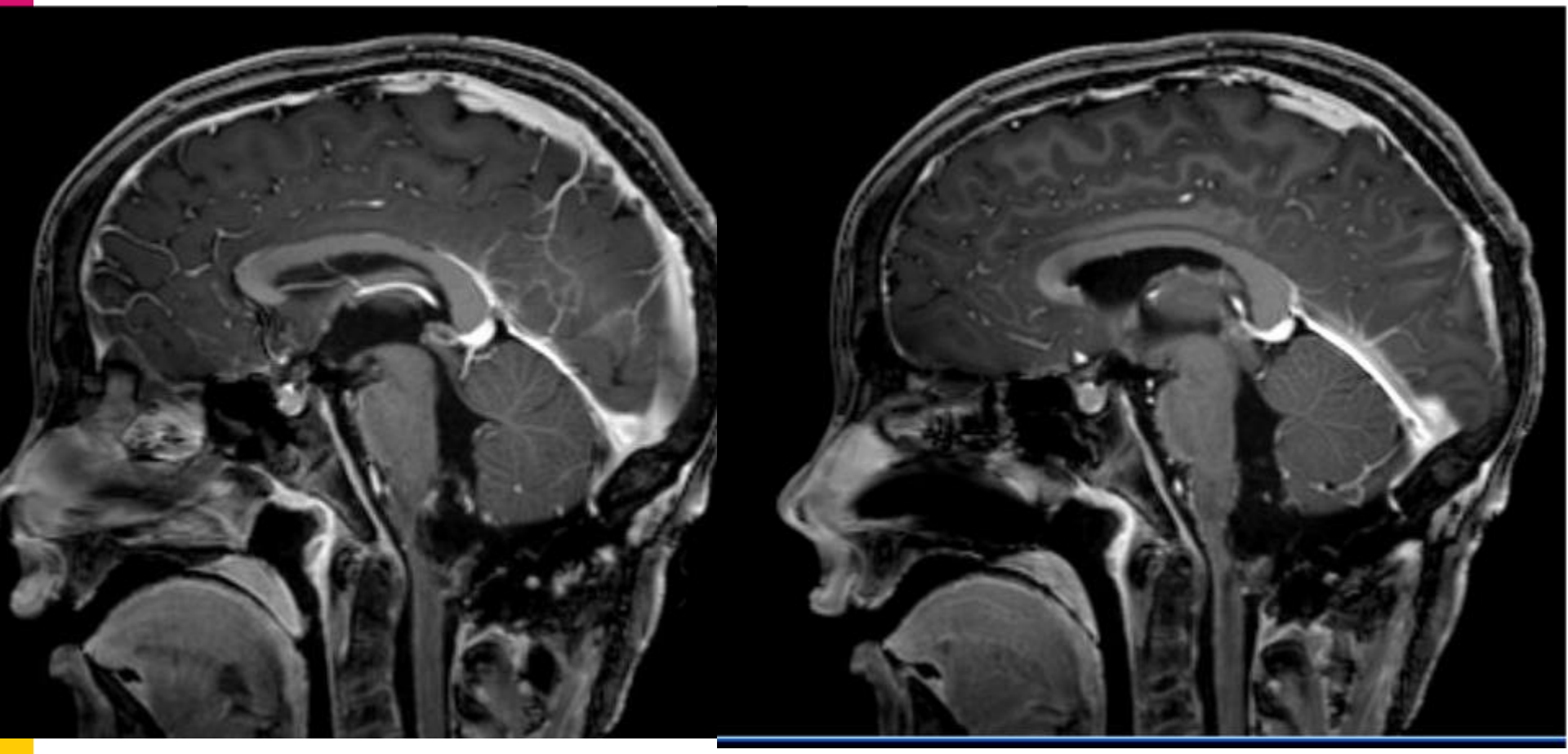
Stimulation intensity: 0.1mA

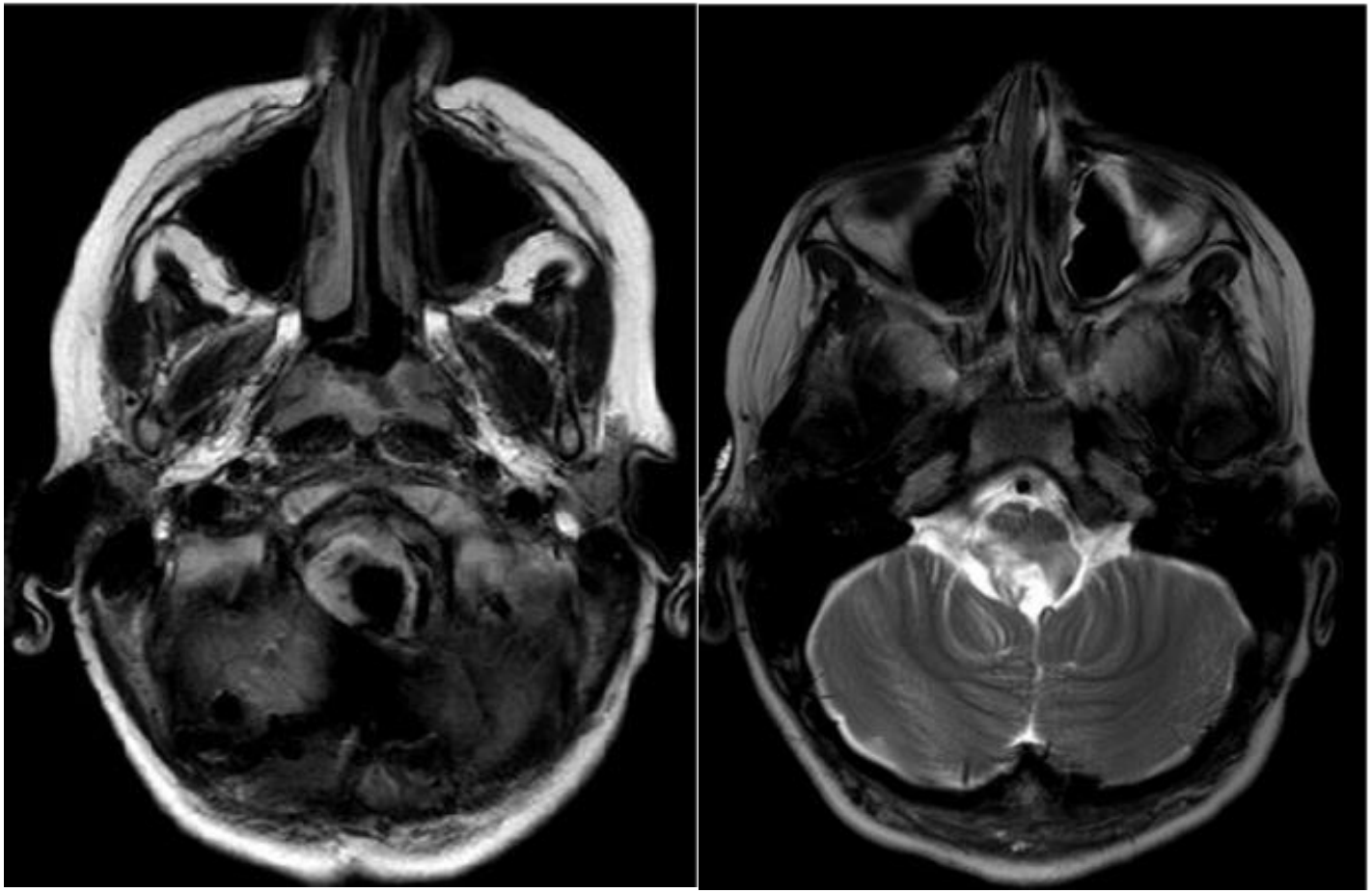






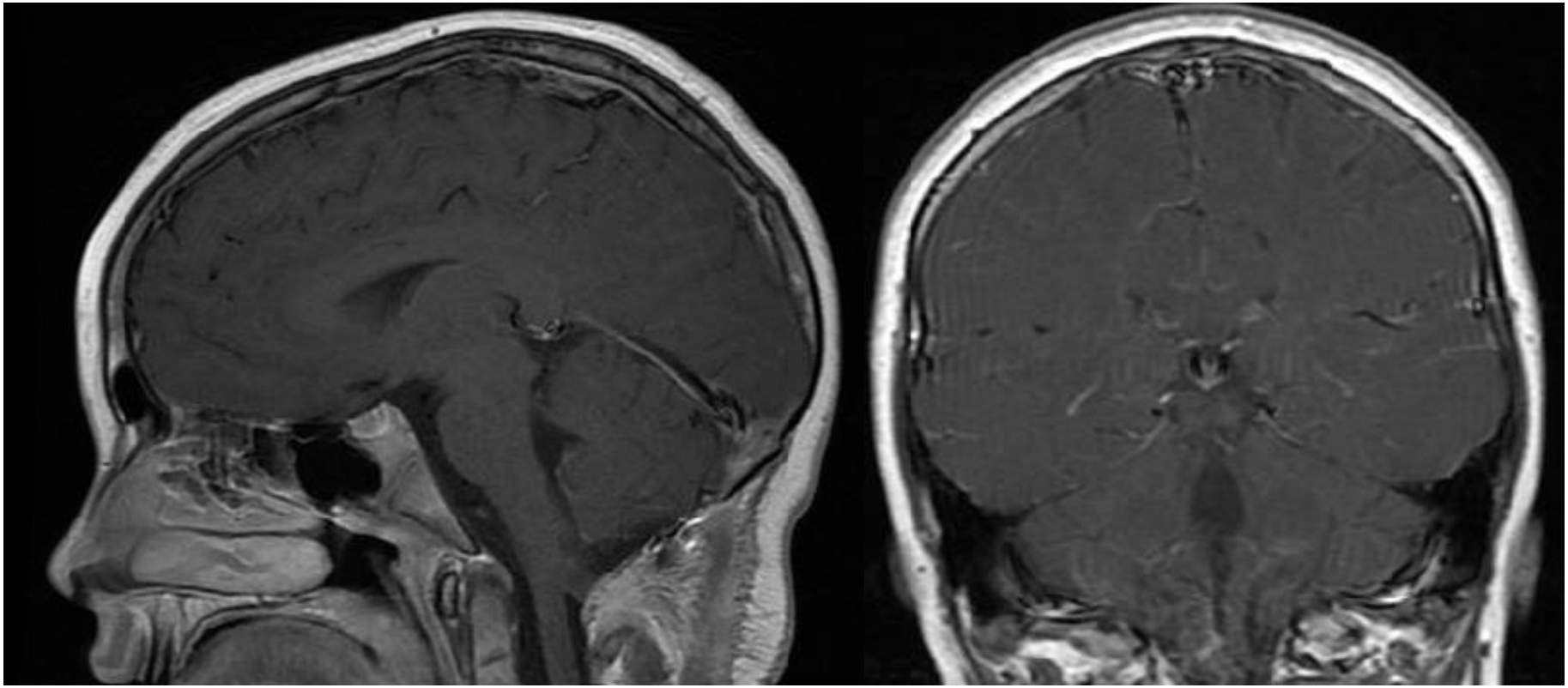
Cranial Nerve Mapping





Postoperative Visit: 2-4 weeks

MRI 3 months Postop



Management of Brainstem Tumors

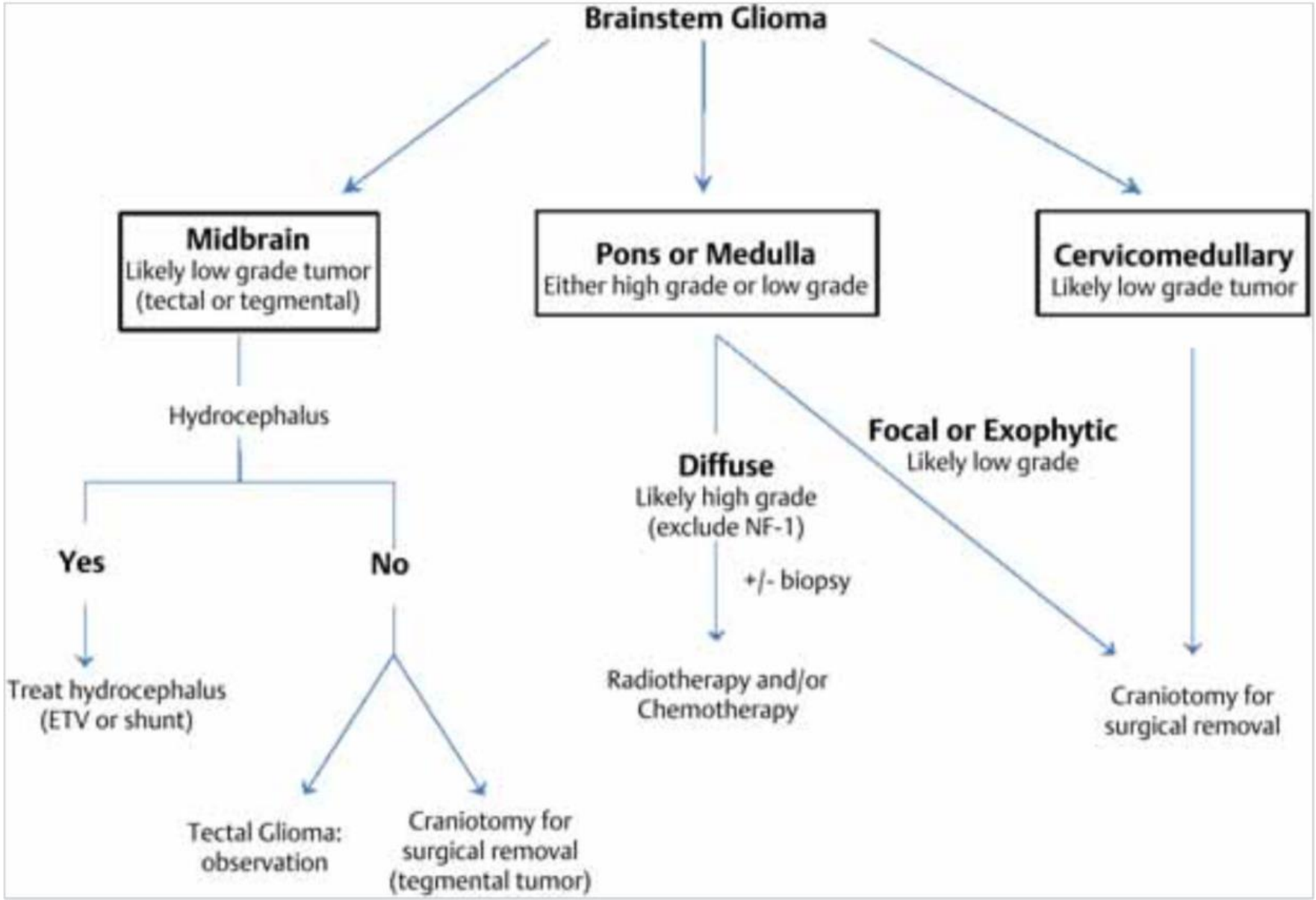


Fig. 20.3 Treatment paradigm for brainstem gliomas.

Conclusions

- Malignant Brainstem Gliomas
  - New Classification (molecular)
  - Role for new treatment modalities
  - To biopsy or not biopsy
- Focal Benign Brainstem Tumors
  - Role of surgery
  - Adjuvant Therapies
    - Radiation- Mainstay Treatment
    - Chemotherapy – Which Agent?